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Volume 311, Issue 5757

COVER

NASA Spitzer Space Telescope false-color image of a portion of the Perseus spiral arm of the Milky Way. Bright regions are clusters of newly formed stars. Recent observations with the National Radio Astronomy Observatory Very Long Baseline Array yielded the distance to a newly formed star (in the bright cluster toward the lower left) with unprecedented accuracy and precisely located the Perseus spiral arm. See page 54.

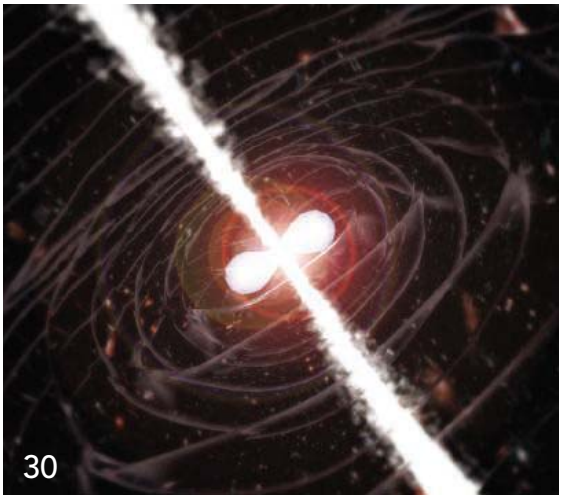
Image: C. E. Woodward, G. Ruch, T. J. Jones

DEPARTMENTS

EDITORIAL

NEWS OF THE WEEK

NEWS FOCUS



CREDIT (BOTTOM LEFT): CAMERON SLAYDEN

LETTERS

BOOKS *ET AL.*

POLICY FORUM

PERSPECTIVES

CONTENTS continued **>>**

Science's 2005 Breakthrough of the Year

Evolutionary Biology

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W. A. SATURNO *ET AL.*

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ARCHAEOLOGY

Early Maya Writing at San Bartolo, Guatemala
W. A. Saturno, D. Stuart, B. Beltrán
An early Maya temple contains hieroglyphics dating to about 250 BC, implying that writing appeared in Maya societies shortly after it emerged elsewhere in the New World.
10.1126/science.1121745

ASTRONOMY

Cosmological Magnetic Field: A Fossil of Density Perturbations in the Early Universe
K. Ichiki, K. Takahashi, H. Ohno, H. Hanayama, N. Sugiyama
Scattering of photons off electrons in the primordial universe generated magnetic fields strong enough to seed magnetic fields seen in galaxies and galaxy clusters today.
10.1126/science.1120690

ECOLOGY

BREVIA: Post-Wildfire Logging Hinders Regeneration and Increases Fire Risk
D. C. Donato et al.
Unexpectedly, by disturbing the soil, salvage logging after a fire in a Douglas fir forest reduced conifer seedling regeneration by 73% and also added kindling to the forest floor.
10.1126/science.1122855

ASTRONOMY

BREVIA: The Orbital Period of the Ultraluminous X-ray Source in M82
P. Kaaret, M. G. Simet, C. C. Lang
Gas supplied from a bloated star orbiting around a massive black hole, a highly transient system that is rarely observed, may periodically brighten a luminous x-ray source.
10.1126/science.1121067

TECHNICAL COMMENT ABSTRACTS

REVIEW

BREVIA

REPORTS

CONTENTS continued **>>**

Introducing Rosetta Elucidator® system. It's a flexible, scalable solution for managing and analyzing large volumes of proteomics data. Powerful and reliable algorithms enable differential protein expression analysis so you can identify and validate potential biomarkers during drug development. Industry-leading tools manage terabytes of data and workflows improve productivity and focus research efforts. The result is an integrated bioinformatics platform that helps you optimize your organization's drug discovery and development process.

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Science

REPORTS *CONTINUED...*

42 & 98

43 & 70

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CONTENTS continued **>>**

2006 NASA Space Radiation Summer School

Applications are being sought for the 2006 NASA Space Radiation Summer School, a three-week course designed to offer graduate students, postdoctoral fellows, and faculty an integrated curriculum of physics, chemistry and radiation biology culminating in hands-on accelerator-based experiments using the synchrotron facility at the NASA Space Radiation Laboratory. Up to 15 students will be selected for the course which begins **June 12, 2006** at the Brookhaven National Laboratory (BNL) on Long Island, New York. Topics will include the physics and biochemistry of charged particle interaction with condensed matter, ionizing radiation dosimetry, DNA damage and repair, genotoxicity measurements, mechanisms of control and loss of cell cycle check-points and apoptosis, signal transduction including bystander effects, genomic instability, neurodegeneration, tissue remodeling and their relationships to carcinogenesis, and degenerative tissue risks including neurobiological damage by space radiation. Course faculty will consist of accelerator physics staff from BNL and biologists and physicists from universities and national laboratories who are actively engaged in NASA space radiation research. A course syllabus and faculty list from 2005 plus additional information may be found at **www.bnl.gov/medical/NASA/summer_school.asp**. Applications for the course may be found at **www.dsls.usra.edu/spacerad/2006/**. Completed applications must be received by USRA DSLS by 5:00 p.m. CT on February 28, 2006. Student selection will be announced by March 15, 2006.

Both foreign nationals and U.S. citizens may apply to the program. All students must satisfy Brookhaven National Laboratory safety and security requirements in order to be admitted. Expenses for travel within the U.S. and for room and board will be covered for those selected for the program. Successful applicants from outside the U.S. must provide for their travel to and from the U.S. Course sponsors are the NASA Space Radiation Health Project, Brookhaven National Laboratory, Loma Linda University, and the Universities Space Research Association. Course directors are Marcelo Vazquez, M.D. of Brookhaven National Laboratory and Gregory Nelson, Ph.D. of Loma Linda University.

Advances in cell signaling.

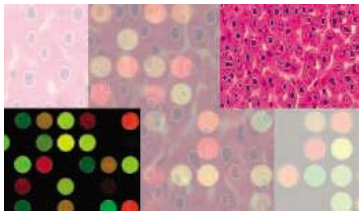
SCIENCE'S **STKE**

www.stke.org SIGNAL TRANSDUCTION KNOWLEDGE ENVIRONMENT

EDITORIAL GUIDE: 2005 Signaling Breakthroughs of the Year
E. M. Adler, N. R. Gough, L. B. Ray
2005 brought exciting advances from signaling molecules to signaling networks.

PERSPECTIVE: The Significance of Interferon-γ–Triggered Internalization of Tight-Junction Proteins in Inflammatory Bowel Disease
H. Chiba, T. Kojima, M. Osanai, N. Sawada
Disruption of tight junctions contributes in intestinal inflammation.

PERSPECTIVE: DNA Damage and Tumor Surveillance—One Trigger for Two Pathways
P. Höglund
The DNA damage response may be activated early in tumorigenesis to stimulate tumor immunosurveillance pathways.



Systemwide searches for biomarkers.

SCIENCE'S **SAGE KE**

www.sageke.org SCIENCE OF AGING KNOWLEDGE ENVIRONMENT

PERSPECTIVE: Biomarkers of Aging—Combinatorial or Systems Model?
A. Kriete
New bioinformatics search strategies might snare elusive biomarkers.

NEWS FOCUS: Uncoupling Insulin
M. Leslie
SIRT1 boosts insulin release by blocking mitochondrial protein.

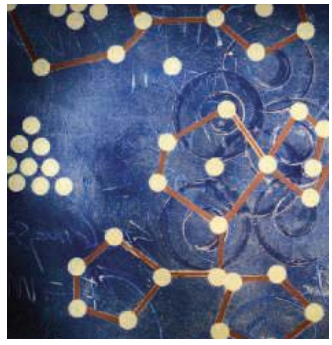
SCIENCE**NOW**

www.sciencenow.org DAILY NEWS COVERAGE

Building a Better Chemical Trap
Cagelike molecules deliver their cargo in a flash.

How to Stop the Munchies
Diet hormone blocks production of appetite-stimulating compounds in the brain.

Irish History Takes a Paternity Test
One in ten Irish men may be related to a famous medieval warlord.



Postdoc opportunities at NIH.

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US: The Intramural Alternative
B. Benderly
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B. Rybarczyk
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UK: A New Resource for Disabled Researchers
M. Mertl
PREMIA is the first UK resource specifically designed for disabled postgraduate researchers.

GRANTSNET: January 2006 Funding News
J. Fernandez
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EDITED BY STELLA HURTLEY AND PHIL SZUROMI

Bring Your Own Bacteria >>

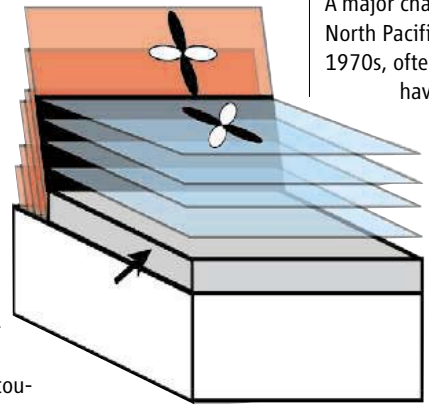
Attine ants of the Americas cultivate gardens of fungi, but these food sources can be parasitized by other fungi. The ants ward off fungal parasites by means of antibiotic-producing bacteria. **Currie *et al.*** (p. 81) now show that the ants are so dependent on the bacteria that they have special anatomical structures that carry the symbionts on the cuticle surface and that may supply nutrients to the bacteria. The organization of these structures varies with the ant species, possibly reflecting variable co-evolutionary pressures.

Money for Nothing

Rarely does one encounter someone who isn't at least slightly interested in money and in how to get more of it in social exchanges. **Camerer and Fehr** (p. 47) review the economic consequences when two kinds of nontraditionally behaving subjects—those exhibiting bounded rationality and those who are nonselfish—enter into games with exclusively self-interested individuals (the completely rational "Economic Man"). It seems that strategic incentives can enable a minority of irrational players to render the entire market irrational, but there are also conditions where a minority of rational traders can make the entire market rational.

Quiet Cuprate Qubits

Macroscopic quantum effects have been reported with a number of conventional (metallic) superconductors. The use of these effects in quantum computing must contend with signal losses caused by decoherence, an inherent problem as the logical elements (qubits) in these systems cannot be uncoupled from its environment. Recent theoretical proposals have suggested ways to isolate the qubit from its electromagnetic environment and make it less subject to decoherence, and the d-wave symmetry of the ceramic high-temperature superconductors (HTSCs) may provide a route to such a quiet qubit. However, it has been assumed that low-energy quasiparticles in HTSCs would destroy any benefits of that environment decoupling. **Bauch *et al.*** (p. 57) now demonstrate an HTSC device with sharp energy levels that exhibits the macroscopic quantum effects seen in their well-behaved metallic cousins. This result also indicates that the dissipation mechanisms in the HTSCs need to be rethought.



Arm's Length

Mapping the dimensions of the Milky Way with precision is still a daunting task. **Xu *et al.*** (p. 54, published online 8 December 2005; see the cover and the Perspective by **Binney**) have used precise images of radio sources in a star cluster to fix the distance to the nearest spiral arm from the Sun using trigonometric parallax, the small shift in apparent position as Earth moves between opposing points in its orbit. Using the Very Long Baseline Array, the authors detected this shift for radio sources in a young star cluster that forms part of the Perseus Arm of the Milky Way. The star cluster has extra anomalous motions beyond the simple rotation of our galaxy about its center that may be consistent with spiral density-wave theory.

Forces Underlying Regime Change

A major change in the marine ecosystem of the North Pacific Ocean that occurred in the mid-1970s, often referred to as a "regime shift," may have been a natural variation in ocean-atmosphere conditions or the result of anthropogenic global warming. **Field *et al.*** (p. 63) examined the abundances of different species of planktonic foraminifera (forams) in sediments from the Santa Barbara channel. Cooler water species began a marked decline in abundance relative to warmer water types around 1960, when deeper penetration of near-surface warming of the ocean began. The proportion of tropical and subtropical forams was not as high any time during the past 1400 years as during the late 20th century. Thus, anthropogenic forcing appears to have been an important component of this regime shift.

Short Stout Snout

Crocodiles evolved during the late Permian and early Mesozoic and became widespread during the Cretaceous, and one common characteristic has been their large, long snout containing numerous teeth. **Gasparini *et al.*** (p. 70, published online 10 November 2005; see the Perspective by **Clark**) now describe an unusual crocodyliform from Patagonia dating to about 140 million years ago. It has a stout head and jaw, but each jaw contains only about one dozen large serrated teeth. This morphology is similar to that of some terrestrial archosaurs and greatly expands the evolutionary morphology of crocodyliforms.

The Making of the Modern Cat

Unraveling the relatively recent speciation events that led to the modern cat family, which includes lions, tigers, clouded leopards, and domestic cats, has been hampered by an incomplete fossil record and a lack of distinguishing skeletal features. **Johnson *et al.*** (p. 73) analyze an extensive array of X-chromosome, Y-chromosome, and mitochondrial DNA sequences sampled from all 37 extant cat species to produce a phylogenetic tree that resolves the eight major lineages of cats. Modern cats appear to have originated in Asia 10 million years ago and undertook a series of 10 intercontinental migrations that correlate with major fluctuations in sea level.

CREDITS (TOP TO BOTTOM): CURRIE *ET AL.*; BAUCH *ET AL.*

Depression, Serotonin, and p11

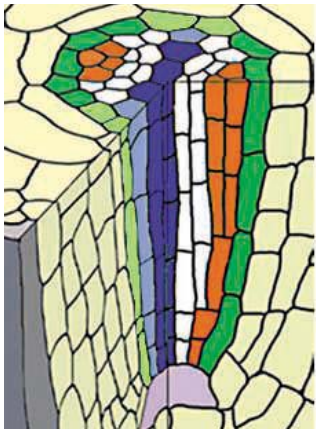
Serotonin is an important modulator in a large number of physiological and pathological brain states. Among the many different serotonin receptors, the 5-HT_{1B} receptor plays a crucial role in regulating serotonin neurotransmission. **Svenningsson *et al.*** (p. 77; see the Perspective by **Sharp**) investigated the role of a protein, p11, which appears to interact with 5-HT_{1B} receptors, in depression and antidepressant treatment. 5-HT_{1B} receptor function depended on p11 expression, and p11 levels were low in depressive states both in animal models (transgenic overexpression and knockout lines), as well as in human postmortem brains from depressed patients. In contrast, p11 levels were increased by antidepressant drugs and electroconvulsive treatment.

But Will You Know Me Tomorrow?

The variety of people with whom we interact extensively changes with time, and a single snapshot cannot provide a complete picture of a dynamic network. **Kossinets and Watts** (p. 88) have used a data set of e-mails between students, faculty, and staff at a large university, in combination with encrypted information about personal attributes and classes attended. They assembled a quantitative picture of how the strength of interactions depends on similarities between the individuals and how the interactions change with time.

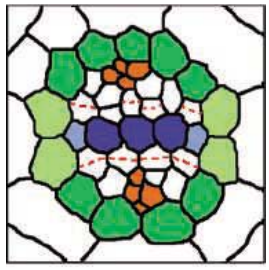
To Grow, or Not to Grow

Adverse growth conditions, such as excess drought and salinity, tend to cause stunted growth in plants. **Achard *et al.*** (p. 91) now show that this growth restraint is an actively controlled process, not simply a by-product of disrupted metabolism. The growth restraint is imposed by DELLA proteins, normally localized to the cell nucleus. *Arabidopsis* has five related DELLA proteins encoded in its genome. The DELLA family of proteins seems to integrate hormonal and environmental signals in order to fine-tune the balance between growth and survival.



Organizing the Root

Specification of cellular fate in the *Arabidopsis* root depends on signaling by the hormone cytokinin. **Mähönen *et al.*** (p. 94) have now analyzed how cytokinin regulates and stabilizes choices in vascular cell fate. Protoxylem differentiation is a default choice, a direction that is blocked by cytokinin. The *AHP6* locus promoted protoxylem differentiation and encodes a protein with resemblances to phosphotransfer proteins except for an amino acid residue critical for phosphotransfer. Nonetheless, it inhibits a cytokinin-directed phosphorelay system. AHP6 expression is spatially localized such that it can block cytokinin function in specific regions, thus allowing protoxylem specification in those locations. Cytokinin and AHP6 interact together in a feedback loop to create specific cellular domains that remain less responsive to cytokinins.



CREDIT: MÄHÖNEN *ET AL.*

Yin and Yang on the Reef

The effects of "no-take" marine reserves remain poorly understood and controversial. **Mumby *et al.*** (p. 98; see the Perspective by **Hoegh-Guldberg**) studied the effects of the recovery of a top predator in a large and long-established coral reef reserve in the Bahamas archipelago. As the predator (the Nassau grouper) increased in abundance, the species composition of its prey (parrotfish) shifted toward species too large and fast to be caught and eaten by the grouper. Parrotfish are a key component of the reef food web because, as algae-eaters, they "clean" the reef of algae and enhance the growth and propagation of corals. Thus, despite increased predator pressure by groupers, coral grazing by parrotfish is enhanced by a shift in the species composition of parrotfish.

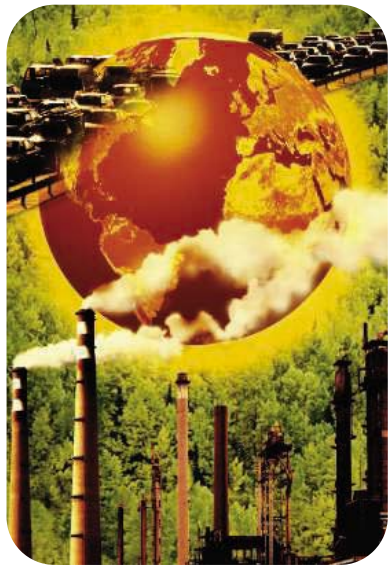
Donald Kennedy is Editor-in-Chief of *Science*.

New Year, New Look, Old Problem

THE NEW YEAR BRINGS *SCIENCE* A NEW LOOK, AND WE HOPE YOU'LL LIKE IT. It also has brought us, our readers, and all Americans another failure to solve an old problem. I'll begin with our redesign and then turn once again, as promised in the last issue, to the refusal of the U.S. government to deal realistically with climate change.

For our redesign, many of my colleagues have been hard at work thinking about design, user-friendly navigation, and related topics. The preparation was undertaken on two tracks: one aimed at restructuring the electronic version of *Science* and the other at creating a new and clearer layout for our print volume. If you are reading this from a monitor, we hope you are already more comfortable finding your way around. I am from the information technology Eocene, so I appreciate any help in navigating the online world. I find the new structure a great improvement and hope you do too.

If you have the print volume in hand, you will see more color-coding of sections, more guidance in the Table of Contents, and a more lively and inviting design—all without decreasing the number of words per page. Particularly where print design is concerned, change can be a dangerous thing, sometimes activating critics who have grown to love the old look. We believe we have made *Science* easier to get around in and more attractive, too. But let us know what you think, with as many specifics as you can.



Now I turn to a different kind of change. For more than two decades, the phenomenon of global warming and its scientific basis have been high-priority objectives for researchers in atmospheric physics and chemistry, oceanography, and paleoclimatology, among others. The consequences of the past century's temperature increase are becoming dramatically apparent in the increased frequency of extreme weather events, the de-icing of the Arctic, and the geographic redistribution of plants and animals.

There is now a broad scientific consensus with regard to the cause. Carbon dioxide and other greenhouse gases (GHGs), largely produced as a result of human enterprises, are responsible for the increase of about 0.7°C in the past century. Models, now running at climate centers in several nations, agree that if we continue business as usual, we may expect a 2° to 5°C increase in the next century. With that, there may be a concomitant rise in sea level and an increase in the weather-related damage that has become a contemporary fact of life.

There is more history than that, but most of those who read this journal know the story. The 1997 Kyoto Protocol laid out some targets and timetables, and although enough nations have now ratified it, the United States has not and has resisted every international effort to reach further agreements. That takes us to Montreal, where a Conference of the Parties has just closed out 2005. The U.S. delegation began by objecting to any setting of reduction targets beyond 2012. When a group of developing countries agreed on the need to reduce tropical deforestation—a major contributor to GHG emissions—potential U.S. participants declined to engage in the discussion. The reasons for this are not entirely clear, though speculations abound.

Thus does the Bush administration keep its record clean: Do nothing except promise voluntary efforts and back long-range research. The climate-denial consortium, supported by a dwindling but effective industry lobbying effort, has staved off serious action. It is a disgraceful record, and the scientific community, which has been on the right side of this one, doesn't deserve to be part of what has become a national embarrassment.

The good news in this department is industry. BP, Shell, General Electric, and hybrid car makers have gotten the message that in the new climate environment, first movers may have the competitive advantage. An investor coalition including CalPERS, the giant California public employers' retirement system, has asked 30 insurance companies to disclose their climate change risks and say what they are doing about them. Actually, the giant reinsurance companies are ahead of them. Swiss Re—imagine this—may be asking holdouts like ExxonMobil this: If you are convinced there's no problem, how about excluding climate risks from your directors' and officers' policies? Good question!

–Donald Kennedy

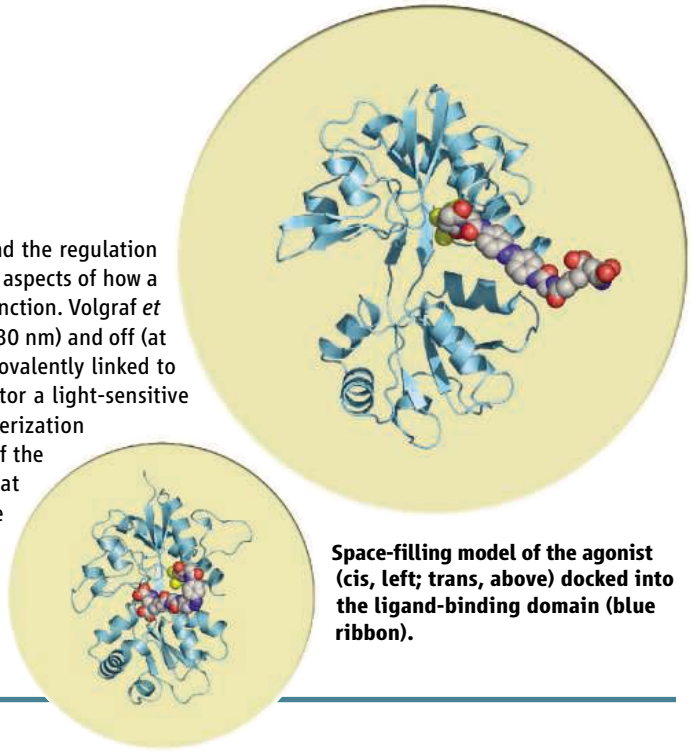
10.1126/science.1123759

BIOCHEMISTRY

A Little Light Work

The interactions of proteins with other proteins (or ligands) and the regulation of protein activity by conformational changes are fundamental aspects of how a wide range of enzymes, signaling proteins, and ion channels function. Volgraf *et al.* describe the design of a channel that can be turned on (at 380 nm) and off (at 500 nm) by light. Using structure-based design, the authors covalently linked to the ligand-binding domain of the ionotropic glutamate receptor a light-sensitive azobenzene derivative with an appended agonist. Photoisomerization (from trans to cis) brings the agonist within striking distance of the ligand-binding site and triggers a conformational change that closes the channel within milliseconds. This approach can be used in future designs of light-operated switches incorporated into a variety of proteins either in electrophysiological settings or in nanodevices. – SMH

Nat. Chem. Biol. 10.1038/nchembio756 (2005).



Space-filling model of the agonist (cis, left; trans, above) docked into the ligand-binding domain (blue ribbon).

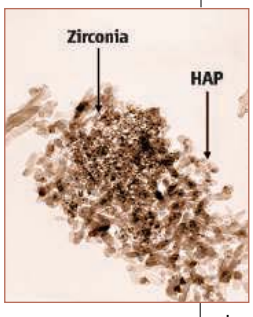
MATERIALS SCIENCE

Stronger Nanocomposites

The use of hydroxyapatite (HAP) in load-bearing orthopedic implants has been limited by its sintering behavior and mechanical properties. Reinforcing agents have been added to make composites, but only HAP-polymer blends have achieved clinical application. For metal and ceramic reinforcing agents, high particle loadings are required, but this reduces the bioactivity. Furthermore, at high loadings of metallic particles, thermal mismatch is an issue, whereas for ceramics, high loading requires high sintering temperatures that degrade HAP.

Using a previously developed nanocrystalline HAP, Ahn *et al.* employed a colloidal technique to add small amounts of zirconia to HAP. Optimal Vickers hardness was obtained for loadings as small as 1.5 weight %, which increased the bending strength by about 30%. Adding the Zr during the precipitation of the HAP achieved an intimate mixing, and the Zr acted as seed nuclei for HAP crystallization. A further benefit was that the composites could be fully sintered under relatively mild conditions, preserving the nanocrystalline grain size of the HAP particles, which have higher bioactivity than coarser-grained ones. – MSL

J. Am. Ceram. Soc. **88**, 3374 (2005).



Electron micrographs of HAP-Zr (3 weight %) composites before (right) and after (left) sintering.

CELL BIOLOGY

Attracting a Blood Supply

Tissue growth and repair require the generation of new blood vessels through the process of angiogenesis. Because cell death and angiogenesis have been shown to be related, Weihua *et al.* examined whether apoptotic cells are involved in initiating the angiogenic response. When apoptotic tumor cells were cultured with endothelial cells, the nonproliferating endothelial cells began sprouting toward the apoptotic cells. As cells go through apoptosis, they display an increase in fixed negative charge on the cell surface, and endothelial cell sprouting was stimulated by this electrostatic interaction. – BAP

Cancer Res. **65**, 11529 (2005).

CLIMATE SCIENCE

Fertilizing Forests with CO_2

One of the biggest obstacles to predicting how much climate will be affected by increasing concentrations of atmospheric CO_2 is not knowing how much additional carbon uptake from the terrestrial biosphere, stimulated by higher CO_2 concentrations, might occur. This sequestration could slow the rate of warming by a significant amount, at least in the short term, so it is important to understand how forests in particular will react to the CO_2 "fertilizer" added by fossil fuel burning.

Norby *et al.* report results from an experiment in which forest stands were exposed to an artificially enhanced level of CO_2 and their net primary productivity (NPP)—the net fixation of C by green plants into organic matter—was determined. NPP increased by an average of 23% over a broad range of productivity when CO_2 was enriched to a level of 550 parts per million (ppm), approximately 170 ppm above today's value and around what it is expected to be by the end of the 21st century. This study thereby provides a foundation on which questions about more specific and subtle responses of ecosystems to CO_2 fertilization, such as how this additional C is allocated and retained in plants and how the availability of other growth-limiting resources might affect NPP, can be addressed. – HJS

Proc. Natl. Acad. Sci. U.S.A. **102**, 18052 (2005).

CHEMISTRY

Unexpected Pairing

It is well known that when chiral compounds crystallize, they often associate preferentially as like enantiomers or as racemic pairs. This property underlies Pasteur's pioneering elucidation of molecular chirality in tartaric acid, and it has since become a useful purification technique for extracting a homochiral sample from a mixture that is enriched in one enantiomer. However, the phenomenon is commonly attributed to the packing forces pertaining in tightly confined crystals; an analogous effect that would lead to loose aggregation in

CREDITS (TOP TO BOTTOM): VOLGRAF *ET AL.*, *NAT. CHEM. BIOL.* 10.1038/NCHEMBIO756 (2005); AHN *ET AL.*, *J. AM. CERAM. SOC.* **88**, 3374 (2005)

solution has been less well-studied.

Soloshonok has found that a trifluoromethyl group at a chiral center can have a surprisingly strong effect in inducing such aggregation during chromatography. Samples of a chiral CF_3-substituted benzamide derivative were eluted on ordinary, achiral silica gel, and initial enrichment of 67% in one enantiomer induced fractionation into a mostly racemic portion and a portion >99.9% enriched in the major isomer. Systematic variation of the compound's substituents implicated the CF_3 group as the critical factor, and further studies confirmed a similar effect in chromatography of several CF_3-substituted alcohols. – JSY

Angew. Chem. Int. Ed. 10.1002/anie.200503373 (2005).

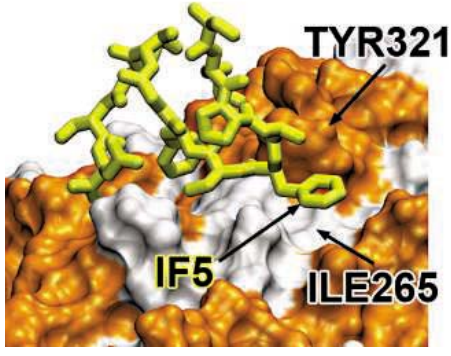
BIOPHYSICS

FinGering the Merchandise

Remarkable advances in the application of physical methods to biological systems have yielded a bumper crop of achievements taken to the *n*th degree, such as atomic-resolution models of enormously complicated macromolecular assemblies and real-time tracking of single molecules within live cells. It is, however, not yet feasible to do both at once, which would allow for the spatiotemporal visualization of protein-protein interactions at the scale of individual amino acid residues, and current approaches have relied on bioinformatics and laborious experimental trials.

Molecular dynamics simulations provide a way to look at these events, and Isgro and Schulten confirm previous results and uncover new ones in their analysis of the nuclear transport factor β-importin and phenylalanine-glycine (FG) repeat–containing peptides; the latter are stand-ins for the nucleoporins, components of the nuclear pore complex that mediates the passage of large molecules (10 to 40 nm in diameter) across the nuclear membrane. FG binding sites on transport factors have been identified in structural and biochemical studies, and proposals for how the nucleoporins gate entry into the nucleus are based on multiple semi-strong sites (1 to 100 nM affinity) that turn the pore into an examination room where import cargoes can be palpated and then accepted or rejected. – GJC

Structure **13**, 1869 (2005).



Interaction of the peptide phenylalanine residue (iF5) with isoleucine (white) and tyrosine (orange) residues of β-importin.

CREDIT: ISGRO *ET AL.*, *STRUCTURE* **13**, 1869 (2005)

Editors' Choice is edited by Gilbert Chin

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<< This Week: Getting Lean with Leptin

Treatment of lean rats with the hormone leptin depleted fat from adipocytes, which of course has raised considerable interest in the possibility of using leptin as a treatment for obesity. However, failure of the hormone to reverse obesity has shown that metabolic regulation needs to be understood better in order to take advantage of its potential therapeutic benefits. Wang *et al.* therefore designed experiments to uncover how white adipocytes are able to store triglycerides at the same time as they secrete leptin at concentrations that, when experimentally administered to lean rats, would block adipogenesis. They identified two mechanisms by which adipocytes from rats fed a 60% fat diet become resistant to leptin. Within 6 days after exposure to the high-fat diet, there was a large increase in the expression of mRNA encoding SOCS3 (suppressor of cytokine signaling 3), an inhibitor of leptin signaling through its receptor (Lepr-b); after several weeks, the level of mRNA encoding Lepr-b decreased. The authors conclude that a high-fat diet causes resistance to leptin signaling in adipocytes and that the hypertrophy and hyperplasia that cause obesity can only occur if such mechanisms allow the adipocytes to ignore the extracellular leptin concentrations to which they are exposed. They further speculate that a period of starvation of patients might reduce such a blockade and allow a beneficial response to leptin therapy in obese patients. – NRG

Proc. Natl. Acad. Sci. U.S.A. **102**, 18011 (2005).

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See pages 102 and 103 of the 6 January 2006 issue or access www.sciencemag.org/feature/contribinfo/home.shtml

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RESOURCES

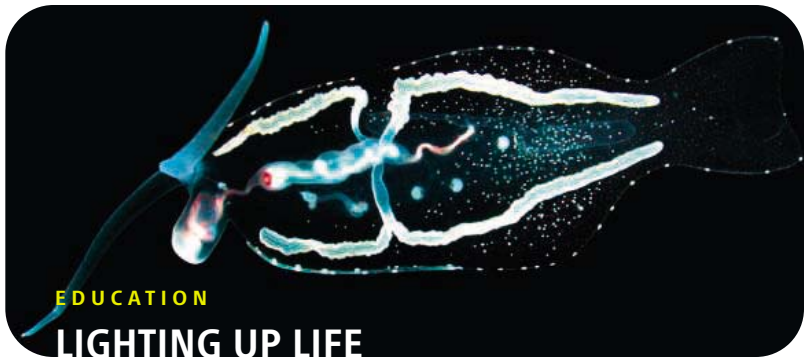
Sniffling Sheep and Coughing Cows

Avian flu has captured the headlines, but it's just one of the animal diseases on the loose. Honeybees can fall victim to mite infestations, for instance, and the viral disease yellowhead decimates farmed shrimp. To corral more information about these and other illnesses, visit the site of the Paris-based World Organization for Animal Health. Weekly announcements furnish the latest on outbreaks. Technical Disease Cards describe the cause, spread, diagnosis, and prevention of 16 major veterinary maladies, such as African horse sickness and vesicular stomatitis, a viral scourge of hoofed mammals. You'll find a list of international experts on particular illnesses and plenty of other resources, including conference reports and disease-prevention guidelines. Above, a cow with foot-and-mouth disease. >> www.oie.int/eng/en_index.htm

WIKIS

Lab Partnering

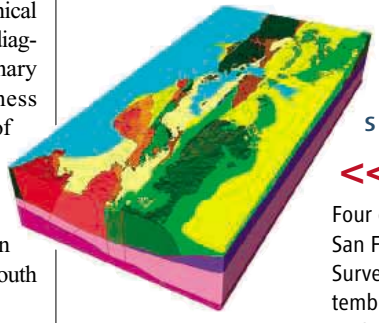
If you've whipped up an irresistible medium for rearing slime molds or collected some tips on performing flow cytometry, share your insights with other biologists at OpenWetWare. This wiki, or user-written collaboration, lets researchers craft virtual meeting places for their own labs or add to communal pages on methods and equipment. Started last year by scientists at the Massachusetts Institute of Technology, OpenWetWare now houses pages from more than 20 labs at 10 universities. Contributions include safety advice for working with ethidium bromide, a reagent for electrophoresis, and a simple protocol for mutating specific nucleotides in a gene. The pages often allow readers to choose among several labs' versions of the same technique. >> openwetware.org/wiki/ Main_Page

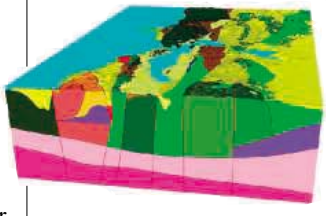


EDUCATION

LIGHTING UP LIFE

Long before Las Vegas imported its first neon tube, bioluminescent organisms such as this nudibranch (*Phylliroe*, above) were putting on the glitz. Find out which marine organisms generate light and how they do it at the Bioluminescence Web Page, hosted by marine biologist Steven Haddock of the Monterey Bay Aquarium Research Institute in Moss Landing, California, and colleagues. Ocean-goers from bacteria to fishes have mastered the light-emitting reaction, in which the enzyme luciferase oxidizes the molecule luciferin. Pages illuminate how some organisms exploit this skill, such as the deep-water fishes that scan their surroundings with red light, which their prey can't see. The site's gallery teems with photos of glowing creatures. For researchers, there's a forum for listing recent publications and announcements of upcoming conferences. Haddock plans to add a link to real-time measurements of bioluminescencing organisms off the California coast. >> www.lifesci.ucsb.edu/~biolum/





SOFTWARE

<< On Shaky Ground

Four earthquakes of at least magnitude six have rumbled through the San Francisco Bay area since 1979. A new model from the U. S. Geological Survey might help seismologists sharpen their predictions of the next temblor's damage. Unlike standard, two-dimensional shaking maps, the simulation renders the upper 32 kilometers of Earth's crust (left), incorporating measurements of the seismic properties of the area's rocks. Because it's three-dimensional, the model includes features such as faults and underground basins that can divert or concentrate a quake's force. Researchers can use the tool to estimate future ground trembling and gauge the power of past, unmeasured events. Download the model here: >> www.sf06simulation.org/geology/

TOOLS

Hooking Up With Antibodies

ExactAntigen can help molecular biologists, immunologists, and other researchers track down everything from samples of the cholera toxin to monoclonal antibodies against the appetite-adjusting hormone leptin. Created by Hanqing Xie of Synatom Research in Ringoes, New Jersey, the free site trolls thousands of Web sites—mainly from commercial suppliers—and other sources to locate providers of antibodies and reagents. Users can search by categories such as gene, organism, and disease. The results often list other molecular products, such as gene-blocking siRNA molecules, along with publications and relevant patents. >> www.exactantigen.com

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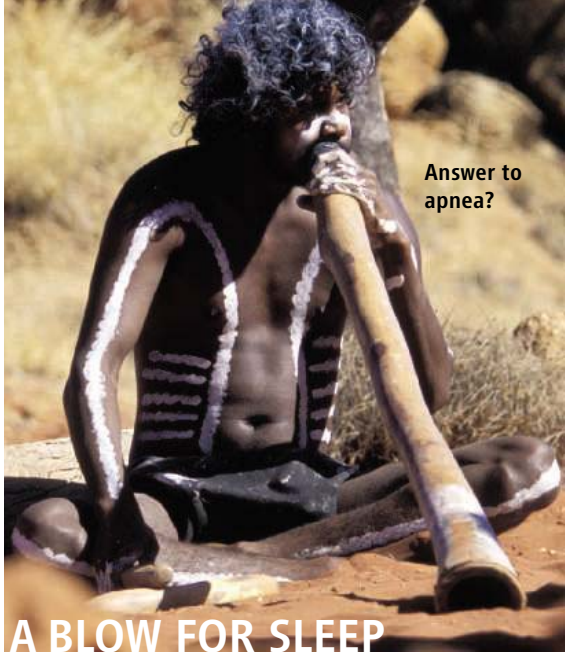

Answer to apnea?

A BLOW FOR SLEEP

Snoring and sleep apnea—brief episodes of nonbreathing—both involve the collapse of upper airways. To keep them open, patients often resort to nose masks that administer pressurized air while they sleep. But a team of Swiss researchers has found that playing the didgeridoo, an Australian aboriginal horn, may be an alternative. Twenty-five apnea patients were randomly assigned to didgeridoo lessons or a waiting list. After four months, the players showed "significant" reduction in daytime sleepiness over the controls, and their sleeping partners reported much quieter nights, the researchers reported online last month in the *British Medical Journal*.

Didgeridoos require an unusual system of circular breathing—the player inhales through the nose while blowing out from puffed cheeks so a sustained note can be held. The researchers speculate that this exercise helps strengthen the muscles in the upper airways.

A New APS >>

The American Psychological Society (APS), which broke off 18 years ago from the American Psychological Association (APA), has now officially put "science" in its name. In a vote put to members, 86% opted to become the Association for Psychological Science. As researchers and science-based practitioners, says Alan Kraut, executive director of the Washington, D.C.–based group, it is APS members who are "the rightful heirs to the traditions of William James … and the other founders of APA."

Kraut says that when the name vote came up, members welcomed the chance to further distance themselves from the APA, complaining that that organization was promoting therapies and coming out with policy statements—such as a stand against the use of Native Americans as symbols for athletic teams—poorly grounded in research. Not so, says APA's Rhea Farberman. "Science and research are the guiding principles of all that APA does."

AN IRISH Y


The "Mound of Hostages" named for Niall.

A study done in 2003 concluded that some 16 million males now living in East Asia could be descendants of Genghis Khan (*Science*, 21 February 2003, p. 1179). Now a group at Trinity College in Dublin has uncovered a similar warlord effect in Ireland.

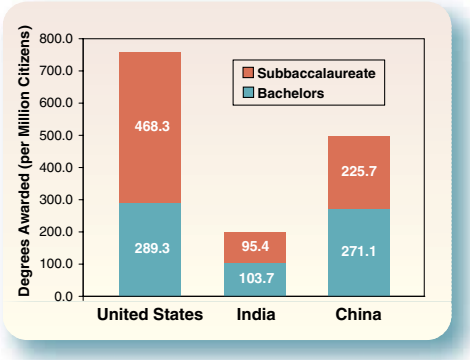
Around 500 C.E., the Irish warlord Niall of the Nine Hostages founded the most powerful ruling dynasty in Irish medieval history, the Uí Néill (literally "descendants of Niall"). A study by geneticist Daniel Bradley and colleagues reveals that this lineage may be imprinted in the genes of roughly a tenth of Irish men living today.

The scientists analyzed the Y chromosomes of 796 Irish men and discovered that many shared a set of DNA markers; this genetic signature was most prevalent in northwest Ireland. It was also strongly associated with surnames tied to the Uí Néill. Judging by mutation rates, the scientists estimated that the men share a male ancestor who lived approximately 1700 years ago—roughly consistent with when Niall lived, the team reported last month in the *American Journal of Human Genetics*.

Geneticist Mark Jobling of the University of Leicester, U.K., says the work "looks pretty convincing," but adds that pinpointing the time of a common ancestor is highly uncertain. The study can't prove that Niall himself had the signature Y; nonetheless, it hints at how a single alpha male can have profound effects on a gene pool.

ENGINEERED NUMBERS?

A new study suggests that data used to bolster claims that the United States is losing its technological edge over other countries are off the mark.



It has been widely quoted that the U.S. awards only 70,000 B.S. engineering degrees each year, whereas India churns out 350,000 and China 650,000. The National Research Council cited the numbers in a recent report on the U.S. need to beef up its scientific talent pool, and senators flogged them last month in introducing a bill to increase U.S. support for science. But a group at Duke University group led by sociologist Gary Gereffi and high tech entrepreneur Vivek Wadhwa suggests that any degree disparity may actually favor the U.S.

After much legwork, the researchers obtained degree data from India's National Association of Software and Service Companies, China's Ministry of Education, and individual universities in both countries. The numbers, it turned out, include information technology and computer science degrees, as well as graduates of 2- and 3-year programs. When the researchers broadened the U.S. definition of engineering degrees accordingly, the U.S. total grew threefold, to 221,000 degrees (memp.pratt.duke.edu/outsourcing). The group also found that India's figures double-counted many students and were based on estimated enrollments, suggesting that 215,000 would be more accurate.

A revised per capita comparison gives the United States a considerable lead over both countries (see graphic, above). Gereffi says that the data don't change the fact that the United States should be concerned about its competitiveness. "I'm not saying we don't have a problem," he says. "All we wanted to do is set the record straight."

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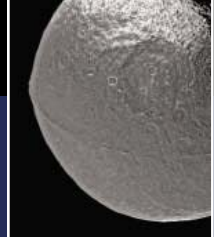
U.S. budget blues
28



Heat source for Saturn's moons
29

STEM CELLS

How Young Korean Researchers Helped Unearth a Scandal . . .

SEOUL AND TOKYO—The announcement delivered a devastating blow to stem cell researchers around the world: On 29 December, a Seoul National University (SNU) investigative team said there was no evidence Woo Suk Hwang and his team had produced any of the patient-specific stem cells they described in a June 2005 *Science* paper. Many Koreans lamented that the revelations dashed the country's hopes for worldwide scientific respect. But the report also vindicated dozens of anonymous young Korean scientists who, without knowing one another, worked together and with the media to unravel a huge scientific fraud.

Two papers published in *Science* by Hwang and colleagues at several institutions in Korea and the United States were hailed as seminal breakthroughs in stem cell research. A March 2004 paper reported the first stem cell line produced from a cloned human embryo. The second paper, published in May 2005, reported the creation of 11 stem cell lines that genetically matched nine patients with spinal cord injury, diabetes, and an immune system disorder. Scientists hope such stem cells could someday lead to insights into many hereditary conditions as well as the creation of replacement tissues genetically matched to patients.

Those hopes, however, began to unravel shortly after midnight on 1 June 2005, when someone sent a message to the "tip off" mailbox on the Web site of a long-running investigative TV news program called *PD Notebook* aired by the Seoul-based Munhwa Broadcasting Corp. (MBC). According to one of the program's producers, Bo Seul Kim, the writer said his conscience had been bothering him over problems he knew of with Hwang's research. Asking *PD Notebook* to contact him, he closed his message by writing: "I hope you don't refuse this offer to get at the truth."

They didn't. When *PD Notebook* executive producer Seung Ho Choi read the message several days later, he asked producer Hak Soo Han to meet the tipster that night. According to Han's recollection of the meeting, the tipster said he had been involved in the research leading to Hwang's 2004 paper in *Science*. He agreed to an interview on tape as long as his identity was concealed, during which he said he had left the team because of ethical and technical concerns. He claimed that despite Hwang's statements to the contrary, some of the eggs used for that research came from junior researchers in Hwang's lab. Producer Kim says the scientist provided names, donation records, and an e-mail message he had received from one of the researchers saying she had donated eggs under pressure from Hwang. The tipster also claimed that based on his knowledge of the team's work, Hwang couldn't have produced the patient-specific stem cells reported in the 2005 paper, although he admitted having no hard evidence of fabrication.

Clear misconduct. Jung Hye Roe, SNU's dean of research affairs, announced that the investigative committee found no evidence of cloned stem cells in Hwang's lab.

CREDIT: JUNG YEON-JE/AFP/GETTY IMAGES

"It was very difficult for me to believe what this person was suggesting," Han told *Science*. But the tipster's documentation of problems surrounding egg donations seemed trustworthy. So Han decided to look into the 2005 paper as well. The producers persuaded two others with inside knowledge of Hwang's lab to help. Han also recruited three scientists from outside the Hwang team as consultants.

Han says the *PD Notebook* team and its advisers began to identify potential problems with the paper, using tactics that they later conceded were journalistically unethical. Claiming they were working on a documentary about Korean biotechnology, *PD Notebook* reporters interviewed co-authors of the 2005 paper and found that the majority had never actually seen the cloned embryonic stem cells. The TV crew also learned from their advisers that teratomas, benign tumors that embryonic stem cells form when injected under the skin of experimental mice, had been produced only for stem cell lines 2 and 3; careful scientists would have produced teratomas from all 11 lines.

Kim says that because one of the informers suggested that the stem cell lines in the 2005 paper could have come from MizMedi Hospital in Seoul, the producers requested and received the DNA fingerprinting data for 15 lines derived at the hospital from embryos created through in vitro fertilization. Through one of their sources, the producers got a sample of stem cell line number 2 and passed it to an independent testing laboratory. The lab found that line number 2 genetically matched a MizMedi line. "Did we actually have evidence that Hwang faked his research?" Han recalls wondering. (SNU would come to the same conclusion months later, announcing on 29 December that stem cell lines 2 and 3 from Hwang's lab came from MizMedi's stem cells.)

Han says he got the news of the lab test results on 19 October while he was in the United States preparing to interview Sun Jong Kim, another co-author of the 2005 paper who had left MizMedi to join the University of Pittsburgh research team led by Gerald Schatten, a Hwang collaborator and co-author of the 2005 paper. In an attempt to

Speak no evil. MBC's initial broadcast on irregularities in egg donation for Hwang's research set off a wave of protests.

CREDIT: KIM JAE-HWAN/AFP/GETTY IMAGES

get an admission of wrongdoing from Kim, Han says, the TV team resorted to some misrepresentation of its own. When the producers met him on 20 October, Han and his partner filmed Kim with a hidden camera; they didn't reply when he asked if they were recording him. In the interview, Han told Kim they had information that could prove Hwang's work was falsified. He also tricked Kim into believing that Korean prosecutors had begun an investigation and told Kim he didn't want to see him get hurt.

On hidden camera, Kim then told Han he followed directions from Hwang to make photographs of two cell lines appear to represent 11 cell lines. The falsified photos appear in the supplementary online material accompanying the 2005 *Science* paper. Han says he now "really repents" their unethical reporting ruses. And those lapses nearly led to their work being dismissed entirely.

But on 11 November, before *PD Notebook* broadcast any of its findings, Schatten announced he was terminating his relationship with Hwang because of concerns about "ethical breaches" in oocyte collection. Schatten emphasized that he was still confident of the research results. On 22 November, MBC broadcast the *PD Notebook* program containing allegations that donors were paid for eggs used in the research leading to the 2004 paper, that junior lab members were among the donors, and that Hwang had lied about the oocyte sources in the *Science* paper. Two days later, Hwang admitted in a press conference that he knew about junior members donating eggs but lied to protect their privacy. He resigned as director of the newly announced Stem Cell Hub but vowed to continue his research (*Science*, 2 December 2005, p. 1402).

Despite Hwang's admissions, *PD Notebook* producers bore the brunt of public anger over the revelations. The backlash intensified after Han and another top producer held a 2 December press conference announcing that a report questioning the authenticity of Hwang's work was yet to come. After Sun Jong Kim and another colleague in Pittsburgh, Jong Hyuk Park, told another television program that the interview with *PD Notebook* had been coerced, all 12 of the *PD Notebook* sponsors canceled their ads, and on 4 December, MBC apologized for the producers' use of unethical tactics.

Producer Kim says that 20,000 angry postings filled up MBC's online bulletin boards, and that the network received so many threatening calls that reporters had a hard time using the phones for work. On 7 December, MBC suspended *PD Notebook* and decided not to air the segment covering questions about the 2005 paper and the interview with Sun Jong Kim.

Given Hwang's popularity among the Korean public and the trust he enjoyed among researchers worldwide, the matter might well have ended there. But, according to an official of the Biological Research Information Center (BRIC), which provides online news on scientific trends and careers primarily for young researchers, at 5:28 a.m. on 5 December, a contributor to a BRIC Internet message board placed a cryptic post with the English header, "The show must go on ..." The anonymous poster suggested that readers look for duplicated pictures among the supporting online material accompanying the 2005 *Science* paper. The poster ended his message with the tease: "I found two! There are rumors that there are more …"

More than 200 posts followed, identifying apparently duplicated photographs. There was also an online discussion about whether someone

Continued on page 25

STEM CELLS

… And How the Problems Eluded Peer Reviewers and Editors

The paper landed in *Science*'s online database on 15 March 2005, a Tuesday. Immediately, the journal's editors recognized a submission of potentially explosive importance. A group in South Korea was describing 11 embryonic stem (ES) cell lines created from the DNA of ailing patients. The advance, eagerly anticipated in the stem cell world, would be a first, and critical to using stem cells to combat disease.

Little did *Science*'s editors, or the nine outside researchers who would examine the paper with varying degrees of scrutiny, realize just how explosive the paper would be. Today, its lead author Woo Suk Hwang stands accused of one of the boldest scientific frauds in memory. Investigators at Seoul National University (SNU), where most of the work was done, announced on 29 December that they could find no evidence of any of the 11 stem cell lines claimed in the paper. On the 10th floor of *Science*'s offices in Washington, D.C., meanwhile, members of the editorial department are spotting problems in Hwang's 2005 paper, as well as another landmark paper from his group published in 2004.

Could *Science* have detected the fraud? *Science*'s editors and many stem cell researchers believe not: The 2005 paper was positively received by its peer reviewers, upon whom *Science* relied heavily to determine whether the paper was worth publishing. "Peer review cannot detect [fraud] if it is artfully done," says Donald Kennedy, *Science*'s editor-in-chief. And the reported falsifications in the Hwang paper—image manipulation and fake DNA data—are not the sort that reviewers can easily spot.

Martin Blume, editor-in-chief of the American Physical Society and its nine physics journals, says that peer review overlooks honest errors as well as deliberate fraud. "Peer review doesn't necessarily say that a paper is right," he notes. "It says it's worth publishing."

That said, *Science*, like other high-profile journals, aggressively seeks firsts: papers that generate publicity and awe in the scientific community and beyond. The practice comes with some risks, critics say, because by definition firsts haven't been replicated. "Is the reviewing looser" on a potentially high-impact paper? asks Denis Duboule, a geneticist at the University of Geneva, Switzerland, who sits on *Science*'s Board of Reviewing Editors. "Frankly, I don't ▶

know." The Hwang paper was accepted 58 days after submission, slightly more swiftly than the average of 81 days.

Science has also not instituted certain policies, such as requesting that authors detail their contributions to a paper or performing independent analyses of images, that some believe might deter fraud. The latter will change in January, when certain images in papers near acceptance will be enlarged and scrutinized by *Science* staffers—a plan in place prior to the Hwang debacle.

After receiving the Hwang paper, *Science* sent it to two members of its Board of Reviewing Editors, who had 48 hours to proffer their opinions on whether it should be among the 30% of papers sent out for review. (The journal later sent the paper to four additional board members.) *Science* declined to identify the board members who vetted it.

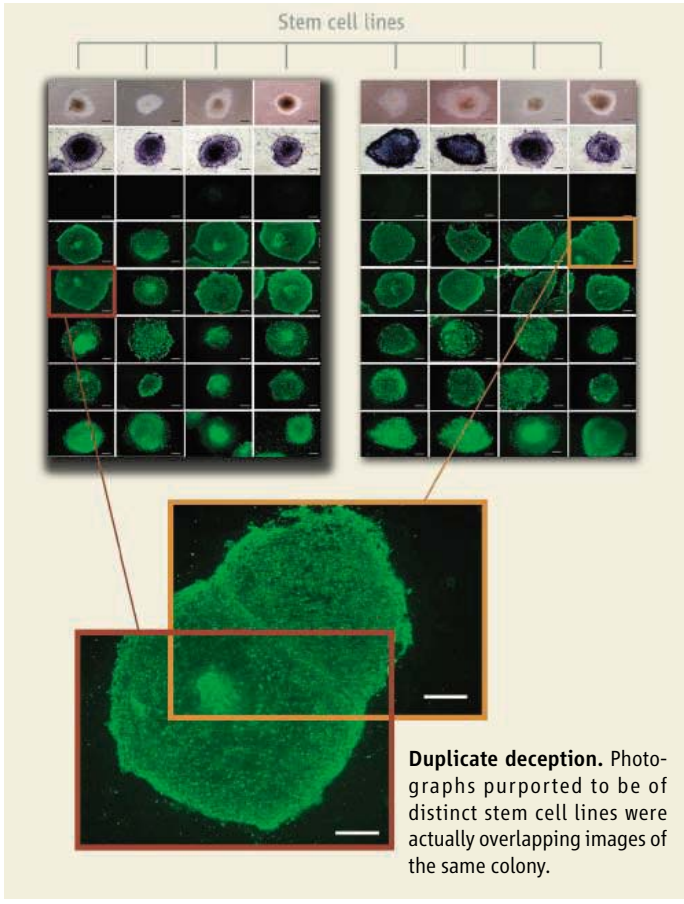
Board members do not inspect a paper's data but instead look for "a mixture of novelty, originality, and trendiness," explains Duboule. On 18 March, after receiving positive feedback from the two board members, an editor sent the paper to three stem cell experts for review. They were given a week, a fairly common time frame.

In this role, "you look at the data and do not assume it's fraud," says one expert who told a *Science* reporter he reviewed the paper on condition that his name not be used. As a reviewer, he says, he sought to ensure that the scientists had identified key markers that distinguish stem cells from other cells and that the DNA "fingerprints" from the stem cells matched those from the patients. The photographs of stem cells and fingerprint data appeared to be in order, he says.

In fact, a number of the images purporting to be of distinct stem cells garnered from patient cells were neither distinct nor from patients. The cells had been extracted from fertilized embryos, the SNU committee alleged, and, in the published version now being analyzed, supposedly different colonies were duplicated or overlapping members of the same ones.

But ES cell colonies often look alike, says John Gearhart of Johns Hopkins University in Baltimore, Maryland, and "you don't really look at a photograph to say, 'That's the same colony turned around.'" A member of *Science*'s Board of Reviewing Editors, Gearhart declines to say whether he examined the paper prior to publication. Even knowing now about the fraud, Gearhart says the deceptions are difficult to spot with his naked eye.

The paper also displayed DNA fingerprints that it claimed were of patients' DNA and genetically matched stem cell lines. Here again, the peer reviewers were fooled. According to the SNU investigation, the analyses were performed solely on samples of the patients' DNA. Only by monitoring an ongoing experiment or analyzing the sample being tested could this deception be unveiled, says David Altshuler of the Broad Institute in Cambridge, Massachusetts, who pored over the DNA fingerprinting data after problems with the paper arose. He says he saw nothing amiss. "The whole issue would boil down to, is the stuff in this tube … from the DNA sample of the donor or the DNA sample of the stem cell line?" says Altshuler.



Duplicate deception. Photographs purported to be of distinct stem cell lines were actually overlapping images of the same colony.

CREDIT: K. BUCKHEIT/*SCIENCE*

Although the flaws in the Hwang paper were especially difficult for reviewers to catch, the peer-review system is far from foolproof, its supporters concede. In 1997, editors at the *British Medical Journal* (*BMJ*) described a study in which they inserted eight errors into a short paper and asked researchers to identify the mistakes. Of the 221 who responded, "the median number spotted was two," says Richard Smith, who edited *BMJ* from 1991 until 2004. "Nobody spotted more than five," and 16% didn't find any.

Some journals have taken steps they hope will keep their pages cleaner. Beginning around 2000, the *Journal of the American Medical Association* (*JAMA*) and other major medical journals began requiring that every author detail his or her contributions to the work. "Obviously, people can lie and cheat, but they have to do it with the knowledge that their colleagues know, and that's a lot harder to do," says *JAMA* Deputy Editor Drummond Rennie, who came up with the idea in 1996. "And later, they have to answer for it."

Although this policy is mandatory at many medical journals, it's voluntary at Blume's physics journals and at *Nature*. *Science* has not adopted this approach. "If the paper is wrong and has to be retracted, then everyone takes the fall," says Kennedy, who believes that detailing contributions can be "administratively complex," and that perpetrators may be less than honest about their contributions.

But some scientists such as Duboule and Gearhart believe *Science* should require authors to describe their contributions. "There should have been some documentation" of who did what on the Hwang project, says Gearhart.

Not only might it now be easier to assign responsibility, but another benefit, says Gearhart, would also be in clarifying the role of a lead author, Gerald Schatten of the University of Pittsburgh in Pennsylvania. Lead authors are often considered responsible for the integrity of the data, and Schatten has come under heavy criticism for acting principally as an adviser to the South Korean group. The University of Pittsburgh has launched its own investigation into Schatten's role in the research.

In the aftermath of the Hwang case, editors at *Science* will be having "a lot of conversations about how we can improve the evaluation of manuscripts," says Kennedy. One thing unlikely to change is the aim of high-profile journals to publish, and publicize, firsts. "You want the exciting results, and sometimes the avant-garde exciting results don't have the same amount of supporting data as something that's been repeated over and over and over again," says Katrina Kelner, *Science*'s deputy managing editor for life sciences. In weighing whether to publish papers such as these, "it's always a judgment call," she says.

But studies are rarely accepted as dogma until they're replicated, says Altshuler, a distinction often lost on the general public—and sometimes other scientists—amid the hype that envelops firsts such as Hwang's paper. Says Altshuler, "A culture that wanted to see things reproduced before making a big deal out of them would probably be a healthier culture." **–JENNIFER COUZIN**

With reporting by Gretchen Vogel.

Continued from page 23

should inform *Science*. Someone did e-mail *Science* editors pointing out the duplicated photos. By that time, however, Hwang had already notified the journal of what he termed an accidental duplication of some of the photos. *Science* editors and scientists around the world were still willing to give Hwang the benefit of the doubt, believing that photos had been mixed up sometime between paper acceptance and publication online.

But the BRIC posts continued. On 6 December, another anonymous BRIC poster wrote that there appeared to be duplications in the DNA fingerprinting traces and posted evidence to support that claim the following day. At about this time, the BRIC postings were reported in the general Korean media and then picked up worldwide. On 12 December, SNU said it would launch an investigation. With public opinion starting to turn, on 15 December, MBC broadcast the *PD Notebook* segment showing Kim—with his face blurred—admitting that he doctored photographs at Hwang's direction. The next day, Hwang and Schatten told *Science* they wanted to withdraw the 2005 paper.

Like most scientists in Korea, Hong Gil Nam, a chemist at Pohang University of Science and Technology and BRIC's first director, has mixed feelings about how the drama has played out. He's sorry to see the scandal unfold but hopeful that the postings on BRIC indicate that "young scientists have a good attitude toward research integrity."

The SNU committee is continuing its work, investigating the legitimacy of Hwang's 2004 paper in *Science* and the group's more recent paper in *Nature* claiming to have produced the first cloned dog. A host of questions remain about whether and when other people at the lab learned about the fraud. Korea's Supreme Public Prosecutors' Office says it is considering a probe of possible criminal activity, pending the outcome of the SNU investigation. The BRIC message board is as lively as ever. And MBC resumed broadcasting *PD Notebook* on 3 January, this time with more people from within Hwang's lab who were willing to talk about what their disgraced boss had done. Among the revelations, *PD Notebook* alleges that Hwang's team collected more than 1600 oocytes from egg donors—not the 427 originally reported—for cloning research for the 2004 and 2005 papers.

–SEI CHONG AND DENNIS NORMILE

With reporting by Gretchen Vogel.

TERRORISM

Indian Scientist Slain in Surprise Attack

HYDERABAD, INDIA—A retired mathematics professor was shot and killed, and four colleagues were wounded, at the Indian Institute of Science (IISc), one of India's premier research outfits, on 29 December. Police have branded the incident in Bangalore a terrorist attack, although as *Science* went to press, no group had claimed responsibility.

The slain scientist, M. C. Puri of the Indian Institute of Technology in New Delhi, was a specialist in operations research, or the use of mathematics to aid in decision-making. Among the injured is IISc's Vijay Chandru, co-inventor of Simputer, a hand-held computing device. The injuries of Chandru and the other victims were not life-threatening.

The attack came without warning on the last day of an international meeting on operations research. "There were no security alerts issued to us," says IISc Director Padmanabhan Balaram. According to eyewitness accounts, at about 7:30 p.m., a single gunman wielding an automatic rifle began spraying bullets into a crowd of scientists filing out of an auditorium after the day's last talk. "A few of us were walking to the next building when we heard sounds like the heavy use of firecrackers," says S. Sadagopan, director of the Indian Institute of Information Technology in Bangalore. On 3 January, police announced the arrest of a suspect: a 35-year-old man who claimed to be a member of Lashkar-e-Taiba, a Pakistan-based militant organization.

Victim. M. C. Puri.

CREDIT: COURTESY OF P. BAGLA

The incident has sent jitters through India's vast R&D establishment. At the annual Indian Science Congress here in Hyderabad this week, police assigned 5000 officers to protect the 5000 participants, including 75 foreigners. And aftershocks are being felt in Bangalore. In addition to IISc, the region, India's Silicon Valley, is home to more than 150 information technology firms, the Indian Space Research Organization, and several high-profile defense labs. The space and defense labs say they have enhanced already tight security. But IISc, with more than 400 researchers and 2000 students, is an academic campus largely open to the public. Balaram says he does not want IISc to become a high-security zone as a consequence of the attack: "The ambience of the university will be lost if you convert it into an armed fortress."

–PALLAVA BAGLA

SCIENCESCOPE

Some Things on the Horizon for 2006:

European Thumbs Green for GM

BERLIN—The new year is looking brighter for European researchers and farmers who want to plant genetically modified (GM) crops. On 14 December, the German government approved the first three varieties of GM maize to be allowed in the country, and a few days later, new agricultural minister Horst Seehofer said he would encourage the planting of GM crops. That's a stark contrast from Seehofer's predecessor, Renate Kunast, who as a member of the Green Party pushed through restrictions on GM planting that researchers said made field trials impossible (*Science*, 25 June 2004, p. 1887).

In late December, the European Commission proposed new rules that would allow organic foods to be labeled as such with up to 0.9% accidental contamination with GM products or seeds from neighboring farms or during processing. Several consumer groups have vowed to fight the proposal to protect what Friends of the Earth Europe says are consumers who want food free of "genetic contamination."

–GRETCHEN VOGEL

Lobbyists Tout Funding Poll

Science boosters believe that the results of a November poll offer one more reason for lawmakers to jump onto the bandwagon this year and increase federal support for academic research—especially if nobody thinks too much about what the answers might mean.

Commissioned by a coalition of business leaders, educators, and professional societies (futureofinnovation.org), the survey reports that 78% of 800 adults, all registered voters, favor spending tax dollars on academic science. Some 70% say they like a key component of one plan being peddled to Congress (*Science*, 21 October 2005, p. 423) that would increase federal funding for the physical sciences by 10% annually for the next 7 years. Support tops 80% among Democrats and those with postgraduate training.

Still, answers to an open-ended question about the value of "university research" revealed some fuzziness about what that phrase actually signifies. One respondent, for example, wrote that "it is very important that young kids get an opportunity [to learn math and science]"; another noted that "education is one of the most important issues we face today."

–JEFFREY MERVIS

ENVIRONMENTAL RESEARCH

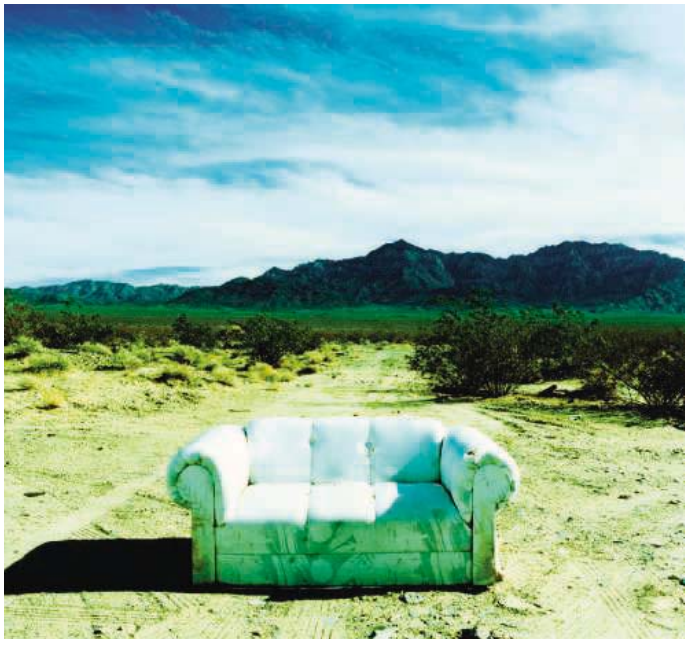
DuPont Settlement to Fund Test of Potential Toxics

The chemicals that make life easier by keeping food from sticking to cookware and blocking stains to carpets and couches also have a darker side: Some of their ingredients don't break down in nature. And the accumulation of these manufacturing aids, called perfluorocarboxylates, is potentially hazardous to humans and wildlife (*Science*, 10 December 2004, p. 1887).

Last month, DuPont, the largest manufacturer of perfluorocarboxylates, agreed to spend $5 million to assess one aspect of the possible risk of exposure. It's part of a record $16.5 million settlement reached last month with the Environmental Protection Agency (EPA), which had accused the company of breaking the law by not releasing health information about perfluorooctanoic acid (PFOA), a perfluorocarboxylate used to make some Teflon products. DuPont has denied any wrongdoing.

The research could potentially lead EPA to require DuPont and other manufacturers to reformulate some products, with a value exceeding $1 billion. "Ultimately, these research results could have a huge influence on regulation," says Scott Mabury of the University of Toronto, Canada.

While welcoming the research, which will involve nine representative DuPont products, some researchers are frustrated by EPA's ground rules. They are particularly upset that the identity of the products to be tested will be kept secret, a decision they say could reduce confidence in the findings and hinder other research into the chemicals. "It really stifles investigation," says Timothy Kropp, a toxicologist with the Environmental Working Group in Washington, D.C. It will also make it harder for outsiders to evaluate and interpret EPA's conclusions, adds Richard Luthy of Stanford University in California.



No rest. Contract labs will test whether stain repellents and related compounds break down into a worrisome environmental contaminant.

The contract labs hired by DuPont will cook each product in a warm brew of aerobic microbes—conditions designed to maximize the chance that they will break down into PFOA or a dozen intermediate metabolites that might suggest that PFOA is a possible outcome. If breakdown products do turn up, says Charles Auer, director of EPA's Office of Pollution Prevention and Toxics, the agency will consider more tests to figure out the rate and extent of the process. (DuPont says that PFOA comes from acci- ▶

SPACE SCIENCE

NASA Terminates Gore's Eye on Earth

NASA has quietly terminated a controversial Earth-gazing science mission left over from the Clinton Administration. Although the satellite is largely complete, space agency officials say they don't have the money to launch and operate the spacecraft, which is designed to provide data on solar storms and the effect on climate of changes in Earth's albedo.

The Deep Space Climate Observatory began life in March 1998 when then–Vice President Al Gore proposed a mission, called Triana, to beam back real-time images of the whole Earth. Ridiculed by Republicans as Goresat, the project was resuscitated after a 2000 report from the National Research Council of the National Academies said it could do important research. But last month, NASA science chief Mary Cleave wrote scientists that "the context of competing priorities and the state of the budget for the foreseeable future precludes continuation of the project."

Originally slated for a space shuttle launch in 2001, the project was delayed and then put on hold following the loss of the Columbia orbiter in February 2003. The following year, however, senior NASA managers informed scientists that the mission remained a priority.

The observatory was designed to hover at a point where the gravity of the moon and Earth cancel each other out, providing a stable platform for observing the sunlit side of Earth on a continuous basis. "We could get an incredible set of data" of the impact of albedo on climate, says Robert Charlson, a climate scientist at the University of Washington, Seattle. The satellite would also have monitored solar storms that pose a hazard to sensitive telecommunications systems.

Grounded. The Deep Space Climate Observatory may never be launched.

Principal investigator Francisco Valero of the University of California, San Diego, says that NASA is ignoring the possibility that the National Oceanic and Atmospheric Administration—which last year requested a study on possible NOAA participation due out next month—could pick up as much as half the cost. "If there is cost-sharing, then the cost could be moderate for each agency," Valero argues, noting that final preparation, launch, and operation of the mission could run between $60 million and $120 million. But NASA's tight budget and the mission's political roots may be too much for scientists to overcome.

–ANDREW LAWLER

CREDITS (TOP TO BOTTOM): PATRIK GIARDINO/CORBIS; COURTESY OF F. VALERO/UNIVERSITY OF CALIFORNIA, SAN DIEGO

dental release during manufacturing, not from the products themselves, and that it has already reduced these emissions by 98% in the U.S.)

The initial observations should increase basic knowledge of these chemicals, says environmental chemist Pim de Voogt of the University of Amsterdam, the Netherlands. EPA plans to review the research protocols with an independent scientific panel, Auer says, and make some of the data public after the 3-year studies are completed. EPA will accept nominations for the panel after naming someone to administer the process.

–ERIK STOKSTAD

ENVIRONMENTAL REGULATION

New Particulate Rules Are Anything But Fine, Say Scientists

Cutting in half the maximum amount of fine particles that people should breathe over 24 hours sounds impressive. But critics of this revision to air pollution standards, proposed last month by the U.S. Environmental Protection Agency (EPA), say the new daily threshold will only marginally improve public health. They say a truly dramatic reduction in mortality rates requires lower annual exposure levels, too. In fact, an outside panel that made such a recommendation is not happy with EPA's decision.

"What is the point of having a scientific advisory committee if you don't use their judgment?" wonders Jane Koenig of the University of Washington, Seattle. EPA Administrator Stephen Johnson didn't answer that question during a 20 December teleconference announcing the standards but said he had thought long and hard about the data. "I made my decision based upon the best available science," he explained. "And this choice requires judgment based upon an interpretation of the evidence."

Studies have shown that inhaling the small particles that make up soot—a widespread byproduct of combustion—harms health, although the mechanisms are not all clear (*Science*, 25 March 2005, p. 1858). Bad air days can trigger asthma attacks, for example, and even kill people suffering from lung or heart disease. Even chronic exposure to lower levels of soot leads to health problems and premature death. In 1997, EPA first regulated fine particles measuring 2.5 micrometers (PM 2.5) or less. As part of a settlement in a suit brought by the American Lung Association, EPA was required to propose revised PM 2.5 rules by the end of 2005.

The new standards would lower the maximum allowable 24-hour exposure for PM 2.5 from 65 micrograms per cubic meter ($\mu g/m^3$) to 35 $\mu g/m^3$. That's within the range recommended by the agency's Clean Air Scientific Advisory Committee (CASAC) but still on the high side. EPA ignored other suggestions, most notably declining to reduce the average annual PM 2.5 standard of 15 $\mu g/m^3$ to 13 or 14.

Such a reduction could make a big difference in public health, scientists have found. EPA models for nine major U.S. cities predict that the tightest daily and annual standards recommended by CASAC would cut the roughly 4700 deaths due each year to PM 2.5 in those cities by 48%. In contrast, death rates would drop by 22% under the agency's proposal to tighten only the daily standard. EPA didn't make a nationwide tally of lives saved under any of the proposals, but epidemiologist Joel Schwartz of Harvard School of Public Health in Boston, using an annual standard of 14 $\mu g/m^3$, came up with 9000 or more. Having a looser standard is "completely unjustified by the science," he says.

Road kill. EPA's proposed regulation of harmful fine particles from buses and other diesel and coal emitting sources doesn't go far enough for some.

CREDIT: JEFF ZELEVANSKY/REUTERS

EPA plans three public hearings on its proposal and will accept public comments until early April. "This isn't over," vows CASAC chair Rogene Henderson of the Lovelace Respiratory Research Institute in Albuquerque, New Mexico, who says the committee will reiterate its case. The final revisions are due out in September.

–ERIK STOKSTAD

Women Get Yen

Female Japanese scientists have something to look forward to in this year's science budget. The plan includes $6 million in new funds for programs at universities and research institutions to help women advance in science and return to work after maternity leave. Reiko Kuroda, a University of Tokyo biochemist, calls the grants "a good start" in tackling the long-standing problem of Japanese women juggling families and science careers.

Elsewhere in the budget, Japanese scientists are feeling relatively lucky, with science-related spending for the fiscal year beginning in April cut 0.1% from current levels to $31.1 billion. Overall government spending will be cut 3%. The budget is pretty good "considering the financial situation," says Kuroda, a member of Japan's advisory Council for Science and Technology Policy. The budget will likely get parliament approval this month.

–DENNIS NORMILE

Congress Joins Paper Chase

Lawmakers are expected this year to consider whether the National Institutes of Health (NIH) should require researchers to send their accepted manuscripts to a free full-text archive.

The voluntary policy, in effect since May, is meant to make freely available the results of NIH-funded studies and guide NIH management. But most NIH grantees aren't cooperating, and proposed legislation could force them to. An NIH advisory panel recently recommended that NIH make submission mandatory and post papers 6 months after publication in journals. The current guideline is 12 months. Many nonprofit publishers prefer that NIH links to the published paper online and warn that a shorter delay could doom journals and bankrupt some scientific societies.

–JOCELYN KAISER

New Indian Centers on Tap

HYDERABAD—India will create 50 new centers for life science and biotechnology research this year that will hire more than 500 scientists over the next 5 years. Buoyed by an economic uptick, the government will also create 1000 positions at the facilities specifically for young researchers. Due to budget restraints, India has not recruited new scientists for government in recent years. Science and Technology department secretary Valangiman Subramanian Ramamurthy, a nuclear scientist, called the new initiative "music for my ears." **–PALLAVA BAGLA**

U.S. SCIENCE BUDGET

NIH Shrinks, NSF Crawls as Congress Finishes Spending Bills

Congressional support for boosting U.S. academic research this year slammed head-on into other national needs and a growing demand to curb federal spending. The resulting crackup has left the National Institutes of Health (NIH) with its first cut in spending since 1970 and the National Science Foundation (NSF) with an increase that only regains lost ground and mocks the recent rhetoric about the importance of a 7-year doubling of its budget.

The wreck is the 2006 budget, the last pieces of which Congress finished just before Christmas in a frenzy of convoluted dealmaking that included a 1% across-the-board cut to make room in a military spending bill for hurricane relief and pandemic flu preparedness. "This is going to be a tough year, and we're going to have to make tough choices," says NIH Director Elias Zerhouni, adding that his highest priority will be to support new investigators. Also facing a tough year is NSF. It was headed for a 3.3% increase but in the end received only 2%. The final figure, $5.58 billion, matches what NSF spent in 2004 and trails the president's request.

Basic and applied research spending across all federal agencies will inch up by $1 billion in 2006, to $57 billion, according to an analysis* by AAAS (which publishes *Science*). But the lion's share of the increase went to preparation for NASA's moon-Mars mission, a bump that helped NASA achieve an overall 1.5% increase, to $16.5 billion. Even a 2.1% increase in the Defense Department's $73 billion research and development budget masks a 2.9% drop in its $1.5 billion basic research account and a flat budget for the $3 billion Defense Advanced Research Projects Agency (DARPA).

In addition to allocating nearly $900 billion in discretionary funding this year, Congress agreed to make $40 billion in cuts over the next 5 years from the much larger chunk of the federal budget devoted to entitlement programs. Student loan programs took the biggest hit, although the so-called budget reconciliation package also contains incentives for low-income college students majoring in science and engineering. It awaits final approval later this month by the House of Representatives.

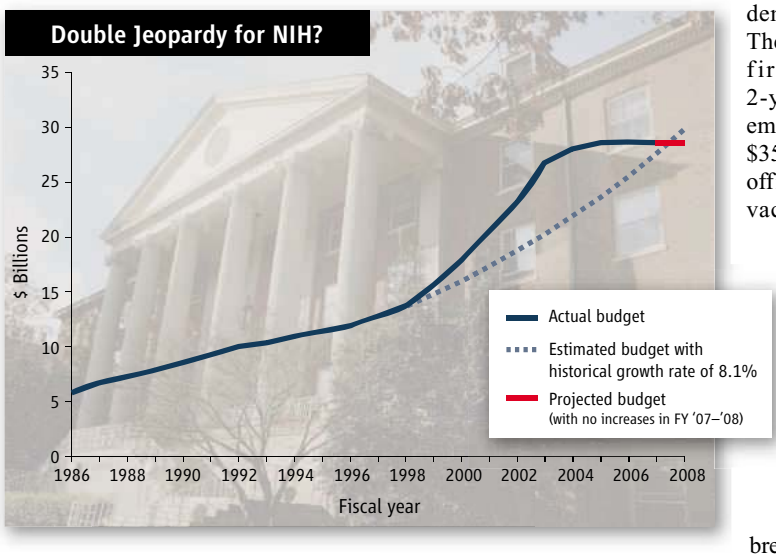
*www.aaas.org/spp/rd

The gloomy 2006 budget news casts a pall over expectations about what President George W. Bush will request next month for the 2007 fiscal year (FY), which begins 1 October. NIH and NSF officials have been told to expect little or no increases, with another cut likely in NSF's education programs and no money for any major new scientific facilities. But last-minute agency appeals were still pending at press time, leaving some officials hopeful that White House budgeteers might be listening to the recent drumbeat of support to boost investment in research and training (*Science*, 16 December 2005, p. 1752).

NASA could again be the favored child in 2007. Even so, Administrator Michael Griffin complained bitterly to the White House in November after officials trimmed by more than half his requested 8.8% increase. Without additional funds for astronomy, earth sciences, and solar physics, Griffin warned, he would be forced "to hold science's budget fixed at FY 2006 levels for the next 5 years." Any moves to scale back NASA's science plans are sure to anger Congress, which last month reauthorized NASA's programs with a warning not to disturb the fiscal balance between science and exploration efforts.

This year's cut in NIH's budget, by $35 million to $28.6 billion, means that the agency is falling behind inflation. That will result in fewer new grants and a continued decline in success rates. A few years ago, NIH funded more than 30% of proposals submitted; this year it will fund 20% or less. Biomedical researchers are "extremely disappointed" by the NIH figure, says Bruce Bistrian, president of the Federation of American Societies for Experimental Biology (FASEB) in Bethesda, Maryland, adding that the cut will force some laboratories to shut down and could displace "some of our greatest current and future scientific talent." Adds Pat White of the Association of American Universities (AAU), "This is the year it's really starting to hurt."

The defense bill, the last spending bill Congress passed before the holiday recess, contains $3.8 billion for pandemic influenza preparedness. The measure funds roughly the first year of the president's 2-year request (*Science*, 11 November 2005, p. 952), including $350 million for states and local officials, $241 million for global vaccine research and surveillance, and $50 million to build lab capacity at the Centers for Disease Control and Prevention in Atlanta, Georgia. Another $2.7 billion could go for steps such as boosting flu vaccine production and stockpiling pandemic vaccines and antiviral drugs.



Going, going … Biomedical lobbyists say flat NIH budgets are erasing the gains from the recent doubling by Congress.

NIH's poor showing since its breathtaking 5-year run ended in 2003 has caused some biomedical lobbyists and researchers to wonder if doubling was such a good strategy after all. FASEB officials have calculated that the biomedical behemoth's budget might soon stand at the same point it would have reached if it had simply continued its historic rate of growth (see graph). In the meantime, scientists would have avoided the roller-coaster ride of the past several years: alluring opportunities followed by a steep drop in success rates for grant proposals and cutbacks in funding promises for future years.

"Certainly, a guaranteed increase of, say, 7% over an extended period would have … allowed for better planning and the better use of funds," says David Bylund, a pharmacology professor at the University of Nebraska Medical Center in Omaha, who contributed to the FASEB analysis. "That said, it is not at all clear that [without the doubling], NIH would be getting larger increases now."

Supporters of a proposed similar doubling for the physical sciences, in particular at NSF and within the science budgets of the Energy and Defense departments, say that NIH's recent experience won't alter their own lobbying tactics. "It's incredibly premature to talk about a backlash to something that ▶

SOURCE: FASEB; PHOTO: NIH

hasn't even begun to occur," says Barry Toiv of AAU, one of several industry and academic groups campaigning for a boost in spending by federal research agencies to bolster U.S. competitiveness.

One early payoff from that campaign is tucked into the budget reconciliation bill. Proposed by Senate majority leader and presidential hopeful Bill Frist (R–TN), it would give $4000 per year to low-income juniors and seniors majoring in science, technology, engineering, and math (STEM) or a foreign language critical to national security. "I like the fact that the money will go to students who are already committed to becoming STEM majors and have demonstrated that they can do the coursework," says Daryl Chubin, director of the AAAS Center for Building Science and Engineering Capacity.

The bill allocates $3.75 billion over 5 years for the initiative, dubbed Science and Math Access to Retain Talent (SMART), and another program that will grant $750 and $1300 respectively to freshmen and sophomores from low-income families, regardless of their major. It will be funded at $790 million in 2006. At the same time, higher education lobbyists are disappointed that the money will come from other programs for college students, one of several features that united Democrats against the measure and required Vice President Dick Cheney's vote to pass the Senate.

–JEFFREY MERVIS

With reporting by Yudhijit Bhattacharjee, Jocelyn Kaiser, and Andrew Lawler.

PLANETARY SCIENCE

How Saturn's Icy Moons Get a (Geologic) Life

SAN FRANCISCO, CALIFORNIA—Why is there geology on Saturn's icy satellites? Where did these smallish moons get the energy to refresh their impact-battered surfaces with smoothed plains, ridges, and fissures? These questions have nagged at scientists since the Voyager flybys in the early 1980s, and the Cassini spacecraft's recent discovery that Saturn's Enceladus is spouting like an icy geyser has only compounded the problem (*Science*, 9 September 2005, p. 1660). Now a group of Cassini team members puzzling over the odd shape of the satellite Iapetus has hit on a possible explanation. Perhaps the moons formed early and grabbed just enough heat-generating radioactivity from the nascent solar system.

At last month's fall meeting here of the American Geophysical Union, California Institute of Technology postdoc Julie C. Castillo, Cassini team member Dennis Matson of the Jet Propulsion Laboratory in Pasadena, California, and four colleagues told how two characteristics of the 1466-kilometer Iapetus—its rotation period and its shape—point to strong early heating. Saturn has obviously slowed the spinning of Iapetus to match the moon's 79-day orbital "year." It did that by gravitationally raising tides in the moon itself that dissipate rotational energy, they noted, just as Earth's moon raises tides in the oceans. In addition, the moon's rapid early rotation left Iapetus with a permanent 33-kilometer high equatorial bulge, first reported last September. Early in its history, the warmer and easily deformed moon must have been rotating fast enough—once every 17 hours or less—for its spinning to raise such a high bulge. As the moon cooled, the bulge "froze" in place.

For the moon's rotation to have slowed from 17 hours to 79 days, even over several billion years, Iapetus must have been warm and therefore pliable long enough for Saturn's tidal forces to slow it, said Castillo. Saturn couldn't have raised large enough tides in a cold, rigid moon. On the other hand, Iapetus couldn't have been too warm too long, or its 17-hour belly wouldn't have gotten stuck that way.

The Cassini group developed a model of a moon's thermal history that takes into account despinning, bulge preservation, and other factors in unprecedented detail. In the model, the only source of heat that would keep the moon pliable for just the right amount of time was the radioactive decay of aluminum-26, a relatively short-lived isotope that left its decay products in meteorites. "We knew it was there," says Matson, but "no one knew how much to put in" their models. Iapetus would have gotten the needed amount if it formed just 1.4 million to 3 million years after the aluminum-26–containing parts of meteorites formed.

CREDIT: JPL/NASA

Midriff bulge. Iapetus spins slowly but sports a swollen equator (topped by a more obvious ridge), suggesting early radiogenic heating.

The history of Iapetus sheds light on the mystery of its sister moon. When Enceladus, too, forms that early in their model, the "dirty ice ball" gets enough heat from aluminum-26 to separate into an icy mantle and a rocky, aluminum-26–rich core. (Its core, Cassini has found, is unexpectedly large.) Then Saturn's tides generate another dose of heat, rather the way repeatedly bending metal does. That tidal heating, along with further radiogenic heating, raises the model core's temperature to 1000 K. That's hot enough to create a deeply buried ocean against the core and probably steam, Matson says, although not enough to make the surface still active today. For that, part of the core would have to melt, forming a weak pocket that would bend with the tides. Then tidal heating could sustain a hot spot on the core and the 8 gigawatts of power Enceladus has been giving out until today, the group calculates.

Aluminum-26 as fuel for icy-satellite heating "is a plausible idea," says planetary physicist William McKinnon of Washington University in St. Louis, Missouri. "I think it's fascinating." But he shares concerns with planetary scientist Francis Nimmo of the University of California, Santa Cruz, about how tightly constrained the result is. "At each stage [of the calculations], there are several knobs you can twiddle," says Nimmo, such as how ice deforms under tidal stressing. "There are so many free parameters it's hard to make a strong statement." The team has examined those uncertainties in analyses yet to be presented, Castillo says, and found they would not substantially alter their conclusion that radiogenic heat warmed Saturn's icy satellites. Their colleagues are awaiting just such a detailed assessment.

–RICHARD A. KERR

Abundant cataclysms studied in 2005 kept astrophysicists tuned to extreme neutron stars in our galaxy and beyond, as well as the most distant blasts yet seen

A Very Good Year For Explosions

IF YOU CATCH THEM AT HAPPY HOUR, AN alarming number of high-energy astrophysicists will admit that they liked to blow things up as children. Nowadays they have graduated to bigger and better things—and blasts. In 2005, in fact, their field enjoyed its most explosive year in decades.

Telescopes caught one startling blast after another, with convulsions on an ultramagnetic neutron star beyond the center of our Milky Way ending 2004 with a bang. Rapid bursts in remote galaxies appeared to come from long-sought collisions between two neutron stars or a neutron star and a black hole. And the most distant explosions ever seen, hailing from the first billion years of cosmic history, marked the deaths of giant stars.

The discoveries marked a stunning inaugural year for NASA's Swift satellite, launched in November 2004 to detect the fleeting explosions called gamma ray bursts (GRBs) (*Science*, 8 October 2004, p. 214). Other satellites and a growing roster of telescopes on the ground—including many new robotic systems—partnered with Swift to observe GRBs and their home galaxies in gamma rays, x-rays, optical and infrared light, and radio waves.

The results, especially the outbursts from neutron stars, yielded vivid insights into the violent universe. "We have hoped for these observations for years," says theorist Stephan Rosswog of the International University Bremen in Germany. Observers were thrilled as well, after years of doubt that they would ever catch up to the transient sky. "If you get onto the telescope quickly enough, you can learn amazing new things about why these objects explode," says radio astronomer Bryan Gaensler of the Harvard-Smithsonian Center for Astrophysics (CfA) in Cambridge, Massachusetts.

The long and short of GRBs

Of all the explosions observed by Swift and its telescopic partners, "short" GRBs garnered the most headlines last year. These pulses of gamma rays, lasting fractions of a second, had eluded explanation for 35 years. "It was an open playing field for theorists," says Edo Berger, a Hubble postdoctoral fellow at the Carnegie Observatories in Pasadena, California. "Then, in just two or three months, we answered the basic questions about them. It was really amazing."

Astrophysicists had been confident that short GRBs erupt from different sources than do "long" ones, which linger many seconds to minutes. Several years ago, research showed that long GRBs arise when the spinning cores of massive stars collapse into black holes. Tight beams of gamma rays tunnel outward through the stars, which then detonate in powerful supernovas visible in optical light. But this messy process is too drawn-out to explain short GRBs.

To account for those bursts, astrophysicists favored quick and deadly mergers of neutron stars: the dense remnants of large stars with cores that fall just short of making black holes. Models of two crashing neutron stars seemed consistent with the sketchy data about short GRBs. Further, astrophysicists had identified neutron-star binaries in the Milky Way and had confirmed that some of them slowly spiral together. Fiery collisions in other galaxies seemed inevitable.

Telescopes caught several such flares in 2005. There were telltale signs of compact mergers: brief gamma ray flashes, no accompanying supernovas, and energies just 0.1% to 1% as prodigious as those of long GRBs. And in three out of four well-studied cases, the short GRBs appeared to blow up in the outskirts of old burned-out galaxies, where stars haven't formed for at least two billion years.

CREDIT: CAMERON SLAYDEN/COSMOCYTE INC.

Contact. At the moment of coalescence, two neutron stars emit fleeting jets of gamma rays before they vanish into a new black hole. Gravitational waves race outward from the whirling crash.

Supernovas have long stopped exploding there, but their shrunken neutron-star remnants could still be slowly converging. The fourth short GRB, spotted on 9 July by NASA's High-Energy Transient Explorer-2 satellite, appeared in a completely different setting: a dwarf galaxy that was still creating new stars. But it could still have come from the same sort of collision, theorists say, because some neutron stars—including a tight binary in our own active galaxy—merge much more quickly if they start out close together.

University press releases and NASA's publicity juggernaut declared that compact binary mergers "solved" the short GRB mystery. But many astrophysicists urged restraint. "Everyone jumped on the neutron star merger bandwagon, but there may be other physical causes," says Neil Gehrels of NASA's Goddard Space Flight Center in Greenbelt, Maryland, Swift's principal investigator.

For one, an unknown fraction of short GRBs may come from neutron stars plunging into black holes. Models suggest that such bursts would display a distinct pattern: flares of x-rays minutes later, as the black hole finishes off debris torn from the neutron star by intense tidal forces. A short GRB that Swift spotted on 24 July emitted such delayed flares, leading NASA to proclaim discovery of a neutron star–eating black hole.

But that's not the only explanation for the July event. Theorist Andrew MacFadyen of the Institute for Advanced Study in Princeton, New Jersey, and colleagues proposed that a single neutron star could suck enough gas from a nearby companion star, creating an object massive and dense enough to form its own black hole. The collapse would spark a short GRB, followed minutes later by x-ray flares as the blast wave struck the parasitized star.

The small number of short GRBs studied in detail so far makes any claims of black holes or other sources tenuous at best, Gehrels agrees. "We think neutron star—neutron star mergers are the most common," he says. "But once we've seen 10 to 100 of these, we'll know a lot better whether any of them stick out as unusual."

LIGO lies in wait

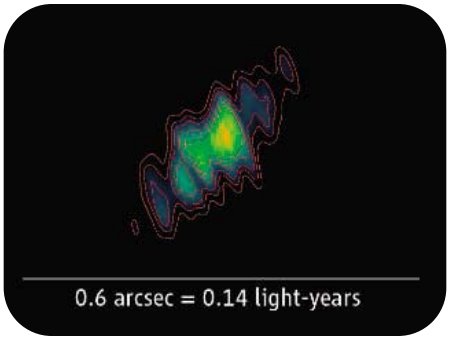
One potential observation at the time of a short GRB would settle all debate: gravitational waves. Einstein's general theory of relativity predicts that inward spiraling binary neutron stars or black holes should distort and ripple the fabric of space-time, producing such waves. The shapes of the resulting waves would depend on the masses of the two objects, the eccentricities of their orbits, and our viewing angle, which affects the patterns of waves we observe. As a result, detecting gravitational waves along with a GRB "would really nail the nature of the compact binary," Rosswog says.

And astrophysicists may finally have the tool to see Einstein's waves. The two facilities of the Laser Interferometer Gravitational-wave Observatory (LIGO) in Hanford, Washington, and Livingston, Louisiana, have reached their promised sensitivities for the project's first phase and will gather scientific data throughout 2006.

"It was an open playing field for theorists. Then, in just two or three months, we answered the basic questions about [short gamma ray bursts]."

–Edo Berger, Carnegie Observatories

At today's sensitivity, LIGO could firmly detect a typical neutron star merger 30 million light-years away, says physicist David Shoemaker of the Massachusetts Institute of Technology in Cambridge. That range extends to 70 million light-years if the viewing angle is good, and even farther if a black hole is involved. "We are certainly optimistic," Shoemaker says. "There is no doubt we are in completely new territory in terms of the probability of observing something."



Out of round. An elongated radio nebula surrounds the magnetar that unleashed a giant flare in December 2004, perhaps betraying the influence of ultrastrong magnetic fields.

CREDIT: VLBA/R. P. FENDER *ET AL.*, 2006 (MNRAS, IN PRESS)

A perfect magnetic storm

Although technically not a 2005 event, an extraordinary outburst on the far side of the Milky Way on 27 December 2004 dominated much of the discussion of short GRBS in the past year. The unusual blast raised the odds that many gamma ray flashes pop off in relatively nearby galaxies—and from radically different sources.

The explosion came from an object about 50,000 light-years away called SGR 1806-20, an exotic neutron star ensnared by the strongest magnetic fields known (*Science*, 23 April 2004, p. 534). Other "magnetars" had erupted with violent flares in 1979 and 1998, but the December event astonished observers. It was brighter than any solar flare, even from its great distance. The x-rays and gamma rays swamped nearly every orbiting detector. Fingernail-sized particle counters on a few satellites kept up with the onslaught, revealing that the explosion released as much energy in a 0.2-second spike as the sun churns out in 250,000 years.

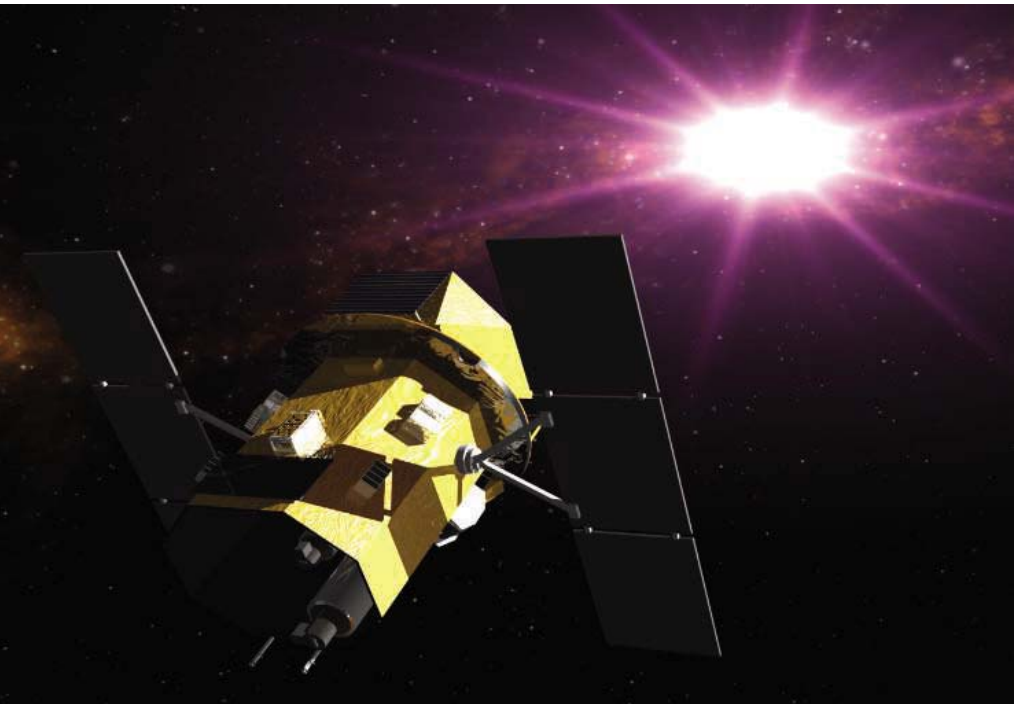
The flare's features jibed with a magnetar model developed in the 1990s by theorists Robert Duncan of the University of Texas at Austin and Christopher Thompson of the Canadian Institute for Theoretical Astrophysics in Toronto. In their scenario, the neutron star's interior is shot through with fantastically tangled magnetic fields, a remnant of the star's youthful spin. Judging by the immense punch from SGR 1806-20, the magnetic field may reach 10^{16} gauss—three times as high as Duncan had previously believed, and 10,000 to 100,000 times stronger than fields on most neutron stars. Over time, the field lines untwist and diffuse toward the surface, forcing the star's magnetized crust to shift. When these shifts become extreme, the entire surface fails and yields. The external field lines, suddenly displaced, whip into new configurations. The implosive release of magnetic tension triggers a blast of gamma rays and other radiation.

Researchers are debating the contents of this blast wave. One clue comes from a nebula expanding into space around the magnetar at 30% the speed of light. High-resolution radio images revealed a surprisingly stretched glowing cloud, created by accelerated particles. "Contrary to expectations, the explosion may not have spread over the entire star," says Bryan Gaensler of CfA. "Material may have been thrown off one side or focused into a jet." Gaensler and his colleagues will use the Very Large Array of 27 radio telescopes in Socorro, New Mexico, on 4 February to scrutinize the nebula's evolving shape.

But evidence suggests that most of the flare's energy didn't emerge in this lopsided particle flow. The blast's initial energy spectrum was nearly that of a perfectly radiating blackbody with a temperature of 2 billion degrees kelvin, Duncan says. "To make that happen you need a clean source of energy from magnetic reconnection, with little matter involved."

Theorist Roger Blandford has a picture of how the 27 December flare proceeded. The magnetar's external fields initially assumed a "smoke ring" geometry used in a spheromak, a prototype of a magnetically controlled nuclear fusion device, says Blandford, director

of the Kavli Institute for Particle Astrophysics and Cosmology in Stanford, California. "If you suddenly release this confined field, it's like an electromagnetic bomb that expands relativistically. There is still some plasma to create the gamma rays, but it's mostly magnetic field." The doughnut-shaped geometry of the magnetic stresses neatly explains the squashed nebula that resulted, he adds.



Another catch. The Swift satellite (artist's conception) has tracked dozens of gamma ray bursts in its first year of operation, including the two most distant explosions yet seen.

The magnetar flare also renewed interest in whether similar events in other galaxies produced many of the short GRBs that Swift and previous gamma ray satellites have observed. Even though the SGR 1806-20 outburst came from a single neutron star, it bears an eerie resemblance to explosions from merging neutron stars, says astronomer Joshua Bloom of the University of California (UC), Berkeley. "If you squint your eyes, they almost look the same." The only difference is that astrophysicists can resolve more details for the Milky Way blast, such as x-ray oscillations possibly due to vibrations of the neutron star's crust.

Astrophysicists now think a short GRB detected on 3 November 2005 was a magnetar flare in a nearby group of well-known galaxies. Astronomer Kevin Hurley of UC Berkeley, who coordinates a network of solar-system probes capable of detecting such flares, believes that extragalactic magnetars produce 1/5 to 1/6 of all short GRBs.

A team in the United Kingdom reached a similar conclusion by examining archival records of short GRBs recorded by NASA's Compton Gamma Ray Observatory, which flew from 1991 to 2000. Astronomer Nial Tanvir of the University of Hertfordshire, U.K., found a modest correlation between the locations of about 500 short bursts seen by the satellite and the positions of galaxies in our neighborhood of the universe, within about 300 million light-years. Although those "local" galaxies are just a tiny fraction of all galaxies in the cosmos, they may have produced 10% to 25% of Compton's short GRBs, the team reported in the 15 December *Nature*. This suggests that magnetar flares—rather than much rarer neutron-star collisions—do indeed account for most of the short GRBs in nearby galaxies.

For Blandford, SGR 1806-20 was the highlight of a rich period in astrophysics. "This was a rather magical thing to happen," he says. "We were lucky to see it with so many telescopes."

The great bright hopes

No luck was involved in the other explosive advance of 2005: GRBs from the era of galaxy formation. Swift has seen two of them so far, most notably a burst on 4 September from a star that died when the universe was just 900 million years old. A 14 August GRB was less well studied but appeared to date to a cosmic age of 1.1 billion years.

Both astrophysicists and cosmologists covet GRBs from even earlier epochs. Astrophysicists hope such primeval bursts will give clues to the types of stars that existed within a few hundred million years of the big bang. The first generation of stars, called "Population III," consisted only of primordial hydrogen and helium. These stars made carbon, oxygen, and heavier elements such as iron, starting the chemical evolution of the universe that continues today. Models suggest that Population III stars were at least 100 times as massive as our sun—huge enough to explode as supernovae (*Science*, 4 January 2002, p. 66). However, physical conditions may have stifled GRBs from the dying stars.

One barrier is the massive envelope of hydrogen in a Population III star. That gas could have acted like a wet blanket, damping the jets of a GRB and preventing their escape when the star's core collapses. New research suggests one way out: If a binary companion strips much of this material, then the GRB blast might break out into space, according to calculations by astrophysicists Volker Bromm of the University of Texas at Austin and Abraham Loeb of CfA.

Bromm and Loeb think Swift's detector might not be quite sensitive enough to spot faint radiation from the earliest Population III GRBs, those that happened within the first 200 million to 500 million years of cosmic time. But if pristine pockets of Population III star formation persisted a few hundred million years later than that, Swift might catch some of their deaths. "Whatever Swift does see, it will help us construct better models of the history of star formation at these times," Bromm says.

Cosmologists are equal fans of Swift, for a different reason: GRBs are ideal probes of the early universe. "For a short time, they are so much brighter than quasars at those distances," says astrophysicist Donald Lamb of the University of Chicago. "They are the great bright hopes of cosmology." Like needle-sharp searchlights, GRBs would illuminate all material along the way to Earth. In particular, cosmologists are eager to learn about how radiation from the earliest stars and galaxies sculpted and ionized the ingredients of the young cosmos. Each distant GRB will expose a bit more of that growth history, Lamb says.

Lamb is optimistic that about 10% of Swift's GRBs will date back to the first billion years of the universe. He thinks a few may even unveil the environment of embryonic galaxies just 500 million years after the big bang. But to take full advantage of the potential science, the largest telescopes on the ground must be ready to gather light before the bursts fade. That hasn't happened yet; for the 4 September GRB, it took 3.5 days for Japan's 8.2-meter Subaru telescope at Mauna Kea, Hawaii, to take marginal data. "We have to get our house in order," Lamb comments.

Still, there's no denying Swift's landmark find. By responding to a faint cry of gamma rays that had journeyed across space for 12.77 billion years, the satellite and its partner telescopes exposed light from the most distant single star yet seen—the type of object that set the stage for a mature universe brimming with violence.

–ROBERT IRION

CREDIT: NASA

Hands-down choice. Colleagues say Michael Anastasio knows the bomb business as well as anyone.

CREDIT: J. MCBRIDE/LAWRENCE LIVERMORE NATIONAL LABORATORY

IN THE NEWS: MICHAEL ANASTASIO

By Design, New Los Alamos Head Hopes to Leave Big Imprint on Lab

Michael Anastasio has spent 25 years at Lawrence Livermore National Laboratory. Now he's bound for its archrival as part of a new team that will manage the troubled nuclear weapons lab

Outside the closed world of nuclear weaponry, Michael Anastasio isn't exactly a household name. But he's quietly risen to become the most powerful scientist in the U.S. weapons complex. Later this year, he will leave his current job as director of the Lawrence Livermore National Laboratory in California to head Livermore's archrival, the Los Alamos National Laboratory in New Mexico. He will be the first person ever to have led both weapons labs.

Anastasio will also be the first director of either weapons lab to answer to a management team that includes several corporations. Since Los Alamos was founded in 1943, the labs have been run solely by the University of California (UC), but on 21 December, the Department of Energy (DOE), the labs' federal overseer, chose a partnership of UC, the Bechtel corporation, and two industrial firms to manage Los Alamos. Insiders say the fact that Anastasio would be the lab's director in the Bechtel/UC partnership helped tip the scales against a bid from Lockheed Martin and the University of Texas. Now comes the hard part—showing that he has the scientific, political, and managerial savvy to reinvigorate Los Alamos as nuclear weapons science arrives at a crossroads.

When he replaces interim director Robert Kuckuck in June, Anastasio will inherit a $2.2-billion-a-year lab whose proud history as home of the world's first atomic bomb has been besmirched in recent years by a succession of scandals related to safety, security, and financial management (*Science*, 27 May 2005, p. 1244). "Mike will have his hands full," said John Gordon, former director of DOE's weapons-focused National Nuclear Security Administration (NNSA). "He stands to be at a pivot."

Anastasio's friends say that few people know the bomb business better than the 57-year-old Washington, D.C., native, and his career has mirrored the evolution of weapon science. He joined Livermore in 1980 with a Ph.D. from Stony Brook University in New York and helped design three weapons in the current stockpile. In 1993, he helped DOE craft its stockpile stewardship program—a $5.4-billion-a-year effort to quantify whether aging bombs would work in war without testing them—and began climbing the management ladder as the stewardship regime took shape. By 2003, his second year as Livermore director, scientists completed a refurbishment of the W87 warhead that extended its shelf life by 3 decades. "In the order of 10 years, we've made some very significant advances," says Anastasio. Without providing details that he says are classified, he points to a "factor of 10" reduction in key uncertainties about aging bombs. Critics dispute such claims, in part because the necessary details are secret.

Observers say that his reputation as a skillful but low-keyed manager could help Los Alamos restore its tarnished reputation. Livermore has experienced fewer safety and security lapses and "is recognized as the best managed [weapons] lab at the moment," says Gordon. Anastasio has also shown an ability to retain the support of his troops despite budget cuts and other unpopular moves, says Bruce Goodwin, Livermore's weapons chief. His first major management task will be to sell Los Alamos employees on a pension plan due out this winter from Bechtel/UC that, under NNSA rules, will be less generous than the current one. Some fear the terms could spark mass retirements, draining the lab of valuable expertise.

Righting the Los Alamos ship will also require him to spend time in Washington, D.C., where he's shown some Beltway panache. "He's not a great briefer, he's not really slick," says former DOE official Victor Reis. "But he answers questions directly." On 6 June 2002, 2 days after he became Livermore's director, the White House proposed changing it into a homeland security lab. Anastasio flew to Washington to protest the idea, which was quietly withdrawn. This year, he successfully fought off congressional attempts to shut down the lab's superlaser, the $3.5 billion National Ignition Facility, after respected scientists questioned whether NIF was meeting its technical benchmarks (*Science*, 2 September 2005, p. 1479).

In his new job, Anastasio will manage a team competing in a congressionally ordered feasibility competition between Livermore and Los Alamos to design replacement warheads. The outcome of that competition will affect the future of the weapons complex for decades. On a day-to-day level, Anastasio will oversee a budget $600 million larger than Livermore's, and a bigger campus.

On the scientific front, he will be moving from interdisciplinary teams that specialize in simulation to a culture known for investigator-driven experimental science. Los Alamos also conducts a broader range of research, a challenge that he promises to address by having UC and its corporate partners work "as an integrated team." And despite several studies that have called for an expansion of plutonium bomb parts manufacturing at Los Alamos, Anastasio says the lab's new corporate management structure "is not a de-emphasis on science."

The Bechtel/UC team's victory last month could mean as much as $79 million a year in management fees if the original 7-year contract is extended for another 6 years. The decision left many pundits speechless, and critics fumed that DOE had overlooked UC's poor record. Department officials clearly liked UC's decision to share management duties with Bechtel, which has managed several nuclear facilities for DOE, and a congressional staffer says that Anastasio and his team helped their cause by thoroughly answering all questions about their proposal. Although healing the storied lab in the coming years will take much more than talk, those who know Anastasio say that he has a knack of coming out on top.

–ELI KINTISCH

Judge Jones Defines Science—And Why Intelligent Design Isn't

In a sweeping decision, a federal district court judge makes the connection between how science operates and the First Amendment

Eric Rothschild says he couldn't be happier with the 20 December decision by federal district court Judge John Jones III ordering the Dover, Pennsylvania, schools to remove references to intelligent design (ID) from the science curriculum. "Our game plan was to explain what science is, so that we could show very clearly that intelligent design was not science. … And the judge got it," says Rothschild, a lawyer with Pepper Hamilton LLP in Philadelphia who helped to represent the parents of 11 Dover students who brought the civil suit. (For a news report on the decision, see http://sciencenow.sciencemag.org/cgi/content/full/ 2005/1220/1).

Holding court. Eric Rothschild fields questions after the judge announced his decision.

The parents sued after the school board passed a resolution in October 2004 declaring that "students will be made aware of gaps and problems in Darwin's theory and of other theories of evolution including, but not limited to, intelligent design." In his ruling, Jones went beyond the question of whether the policy was religiously motivated and tore into the whole foundation of ID. His 139-page decision,* which incorporates substantial portions of the plaintiffs' arguments, also castigates the school board for the "breathtaking inanity" of its policy.

The winners hope the decision will end the ID debate in Dover: Eight of the nine members of the school board were defeated in a November election by candidates opposed to the ID statement, and the new board has said it doesn't plan to appeal the ruling. But it isn't expected to end attacks on evolutionary theory by supporters of the view that the complexity of life requires a supernatural designer, say scientists and those who have followed the bitter debates. "ID is like a waterbed," quips Eugenie Scott of the National Center for Science Education in Oakland, California, which tracks the issue. "If you push it down in one place, it pops up in another place."

In the following excerpt, Jones mentions two important cases—*Edwards v. Aguillard*, a 1987 Supreme Court decision, and *McLean v. Arkansas Board of Education*, a 1982 district court decision—that set down a national prohibition against the teaching of "creation science" in public schools. He also refers to plaintiffs' witness Kevin Padian, a paleontologist at the University of California, Berkeley, and defense witness Michael Behe, a biologist at Lehigh University in Bethlehem, Pennsylvania.

–JEFFREY MERVIS

*http://www.pamd.uscourts.gov/kitzmiller/kitzmiller_342.pdf

Excerpts from the decision >>

ID is not science. We find that ID fails on three different levels, any one of which is sufficient to preclude a determination that ID is science. They are:

1) ID violates the centuries-old ground rules of science by invoking and permitting supernatural causation;

2) The argument of irreducible complexity, central to ID, employs the same flawed and illogical contrived dualism that doomed creation science in the 1980s, and;

3) ID's negative attacks on evolution have been refuted by the scientific community. … It has not generated peer-reviewed publications, nor has it been the subject of testing and research. …

ID takes a natural phenomenon and, instead of accepting or seeking a natural explanation, argues that the explanation is supernatural. … It is notable that defense experts' own mission is to change the ground rules of science to allow supernatural causation of the natural world, which the Supreme Court in *Edwards* and the [district] court in *McLean* correctly recognized as an inherently religious concept. … Not a single expert witness over the course of the 6-week trial identified one major scientific association, society, or organization that endorsed ID as science. What is more, defense experts concede that ID is not a theory as that term is defined by the National Academy of Sciences. …

ID is at bottom premised upon a false dichotomy, namely, that to the extent evolutionary theory is discredited, ID is confirmed. This argument is not brought to this Court anew, and in fact the same argument, termed 'contrived dualism' in *McLean*, was employed by creationists in the 1980s to support 'creation science'. … However, we believe that arguments against evolution are not arguments for design. Expert testimony revealed that just because scientists cannot explain today how biological systems evolved does not mean that they cannot, and will not, be able to explain them tomorrow. …

The concept of irreducible complexity is ID's alleged scientific centerpiece. Irreducible complexity is a negative argument against evolution, not proof of design. Irreducible complexity additionally fails to make a positive scientific case for ID. … As expert testimony revealed, the qualification on what is meant by 'irreducible complexity' renders it meaningless as a criticism of evolution. In fact, the theory of evolution proffers exaptation as a well-recognized, well-documented explanation for how systems with multiple parts could have evolved through natural means.

Exaptation means that some precursor of the subject system had a different, selectable function before experiencing the change or addition that resulted in the subject system with its present function. For example, Dr. [Kevin] Padian identified the evolution of the mammalian middle ear bones from what had been jawbones as an example of this process. By defining irreducible complexity in the way that he has, Professor [Michael] Behe attempts to exclude the phenomenon of exaptation by definitional fiat, ignoring as he does so abundant evidence which refutes his argument. …

We find that ID is not science and cannot be adjudged a valid, accepted scientific theory. … [It] is grounded in theology, not science. … It has no place in a science curriculum. ID's backers have sought to avoid the scientific scrutiny which we have now determined that it cannot withstand by advocating that the controversy, but not ID itself, should be taught in science class. This tactic is at best disingenuous and, at worst, a canard. The goal of the ID movement is not to encourage critical thought, but to foment a revolution that would supplant evolutionary theory with ID.

CREDIT: ASSOCIATED PRESS

LINGUA FRANCA. Now, the hard work begins. As the first director-general (DG) of the International Thermonuclear Experimental Reactor (ITER), veteran Japanese civil servant Kaname Ikeda needs to bind up any wounds from the bruising 16-month fight over hosting the $12 billion reactor before moving ahead. Japan was allowed to nominate the first DG in return for ceding victory to the European Union's proposed site at Cadarache, France. At a ceremony opening the ITER Joint Work Site office at Cadarache last month, Ikeda spoke in French about how happy he was to be there. He remains Japan's ambassador to Croatia until the ITER implementation agreement is signed, which is expected early this year.

2006 PEOPLE to WATCH

PUBLIC HEALTH REVAMP. Julie Gerberding, head of the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, is expected to wrap up a painful overhaul of the agency this year that may affect the bottom lines of division directors. An AIDS researcher who took the helm of CDC in 2002, Gerberding will reshape budget priorities according to "health protection goals" that CDC unveiled last year. The impact of those goals on research could determine whether the agency can rebuild its ranks after a string of departures by senior scientists.

CRISIS MANAGER. Nearly three years after the SARS outbreak, China is once again at the center of global efforts to monitor an emerging disease. And one of the people who helped restore the country's credibility in 2003 is now being counted on to keep abreast of avian influenza. Health Minister Gao Qiang will have to do his best to convince the global community that China is accurately tracking human cases. An economist long attached to China's Ministry of Finance, Gao was tapped to be executive vice minister of health when top managers were replaced for mishandling the SARS crisis and stepped up to minister last spring.

A SMALLER CROP. Taking over the smaller European Commission's directorate for research could be something of a holiday for José Manuel Silva Rodríguez. An agricultural engineer from Madrid, the 56-year-old Silva Rodríguez has been director general for agriculture, placing him in charge of the Commission's biggest spending department. Nonetheless, there's plenty to do on the research front, including moving ahead with the ITER fusion reactor in France, being midwife to the European Research Council, and settling on a 7-year budget for European Union research.

DOUBLE TROUBLE? Andrew von Eschenbach faces mounting pressure to quit one of the two jobs he's juggling—director of the National Cancer Institute (NCI) and acting commissioner of the Food and Drug Administration (FDA). Cancer advocacy groups, researchers, and some legislators have questioned whether one person can handle both positions and whether the head of FDA, which reviews cancer drugs studied by NCI, should have ties to the institute. Von Eschenbach has taken a leave of absence from NCI, but insiders say he still shows up at the agency and makes key decisions. It's unclear whether the Bush Administration plans to name a permanent FDA commissioner anytime soon, however, or who that person will be.

A PASTORAL PASTEUR? Researchers at the Pasteur Institute say the atmosphere has improved since Alice Dautry-Varsat, the first woman to head the famed Parisian lab, took over on 1 October. The infighting and widespread discontent that plagued her predecessor, Philippe Kourilsky, has ended, they say. But Dautry-Varsat and her new management team still have a lot to do, including refurbishment of Pasteur's aging campus and figuring out how to keep the institute among the scientific elite.

CREDITS (TOP TO BOTTOM): CLAUDE PARIS/AP PHOTO; CDC (2002); WWW.TOUROFHOPE.ORG; WILSON CHU/REUTERS; INSTITUT PASTEUR; EUROPA

Path to the laser 39

Restoring the reefs 42

LETTERS

edited by Etta Kavanagh

Editorial Expression of Concern

THE REPORT ENTITLED "PATIENT-SPECIFIC EMBRYONIC STEM CELLS DERIVED FROM HUMAN SCNT blastocysts" by W. S. Hwang *et al.* (*1*) reported the establishment of 11 human embryonic stem cell lines by somatic cell nuclear transfer of skin cells from patients with disease or injury into donated oocytes. Hwang and G. Schatten, the corresponding authors of the paper, have notified *Science* of their intention to retract the paper. Hwang has sent us some language that he intends to use in the retraction. We have requested more information from the authors as well as agreement from all the co-authors to retract the paper.

On 23 December 2005, the Seoul National University Investigation Committee provided an interim report on their investigation of Woo Suk Hwang's research. The report (*2*) stated that "the experimental data submitted to *Science* in support of 11 stem cell lines (DNA fingerprinting, microscopic photos, confirmation of teratomas, etc.) were all derived from 2 cell lines" and that "the Committee finds that the experimental data published in the 2005 *Science* paper were based on a deliberate manipulation, in other words a fabrication of research results." The report also states that "The Investigation Committee has submitted samples of cell lines 2 and 3 for DNA testing in order to determine their authenticity."

An earlier paper by Hwang and colleagues (*3*) attracted much attention as the first demonstration of the derivation of a pluripotent embryonic stem cell line from a cloned human blastocyst. Given the concerns raised about the 2005 paper, we are undertaking a careful review of the 2004 paper as well and expect to consult with outside advisers as needed. The SNU Investigation Committee announced that it has begun an investigation of this paper and of other work from the Hwang lab.

Science is publishing this expression of concern to alert our readers that serious concerns have been raised about the validity of the findings in these two papers. We are working with the authors and SNU to proceed with the retraction of the 2005 paper (*1*). We will provide more information on the 2004 paper as it becomes available.

DONALD KENNEDY

Editor-in-Chief

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Revamping NIH Study Sections

ANTONIO SCARPA, DIRECTOR OF NIH'S CENTER for Scientific Review, has stated his intention to enhance efficiency and recruit excellent reviewers for NIH peer review. As an NIH grant holder for 30-odd years and former study section member, I propose the following.

Every NIH grant holder above the rank of assistant professor should be required to serve on an NIH study section once a year. It would be a responsibility, like jury duty; those too busy to serve would be presumed incapable of effectively administering a grant. Actual service time would likely be considerably less. A normal study section load of 10 to 12 grants would thus require service only every other year.

Advantages would be the following:

1) Experienced senior scientists would be brought back into the system. Inexperienced assistant professors would be removed, to their own great benefit. The quality of scientific review would immediately improve.

2) The onerous workload of a full-time study section member would be eliminated.

3) Peer review would become less political. Each study section tends to develop its own subculture, but this is not necessarily a good thing. A study section's task is to identify for NIH those projects of greatest scientific merit. A fresh look at a revised proposal by a new panel of peers will maintain focus on its fundamental significance and avoid overemphasis on subculture-sensitive details.

One frequently voiced objection is that such required service will be performed grudgingly and therefore badly. But most of us will adhere to accepted professional standards, even when performing an onerous task. Further, the study section acts as its own peer reviewer; nobody wants to present an incompetent critique before peers.

Such "full participation" would correct some of the distortions that threaten to overwhelm this basically admirable process.

JOHN LENARD

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Clarifications on miRNA and Cancer

THE NEWS FOCUS ARTICLE "A NEW CANCER player takes the stage" (4 Nov. 2005, p. 766) by J. Couzin on miRNAs and cancer has a quote from me that has been taken out of context and conveys exactly the opposite meaning of my unedited comments.

To clarify, some of the miRNAs induced during cell differentiation may down-regulate cell division programs. Because miRNAs down-regulate target mRNA genes through complementary sites in their 3′ UTRs, oncogene targets with mutations in miRNA-complementary sites might escape miRNA regulation to generate dominant activating oncogene mutations. Such gain-of-function mutations are seen in plant genes that regulate cell division at the meristem.

Other miRNAs are overexpressed or amplified in animal tumors, suggesting that these miRNAs negatively regulate tumor suppressor or proapoptotic genes.

Many dominant oncogenes have been revealed by cell transformation assays over the past 30 years. If miRNA negative regulation of oncogenes is a key element in cancer etiology, I am surprised that 3′ UTR mutations in oncogenes were not detected in such transfection experi-

ments. In addition, I would have expected the miRNA genes that target tumor suppressor genes to have been recovered in such transformation experiments. These RNA genes may not have been recognized as encoding miRNAs and the oncogene 3′UTRs may not have been recognized as miRNA targets, but I would have expected the oncogene canon of today to have included more regulatory RNAs and mention the importance of 3′UTRs as sites of oncogene regulation.

I expressed to Couzin my belief that "I just find it hard to believe that the cancer people were that lame" to have missed such mutations in 3′ UTRs by only sequencing open reading frames of oncogenes, or to have missed regulatory RNA genes because they dropped the study of oncogenes without open reading frames. The quote in this context has precisely the opposite meaning to its use in the article. The more likely reason why so little evidence for miRNAs emerged from previous oncogene genetics is that the fibroblast cell transformation techniques used to detect dominant oncogenes systematically failed to detect miRNA-based regulatory defects, for example, because the 3T3 fibroblasts may be deficient in components essential for miRNA-based regulation, because the miRNA-based gene activations are not strong enough to bypass other cell cycle controls, or because miRNAs are modulatory to oncogenes but are not central to tumor initiation or progression.

GARY RUVKUN

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Coastal Vegetation and the Asian Tsunami

THE BARRIER FUNCTION OF COASTAL VEGETATION during the recent tsunami disaster has been highlighted by the results of F. Danielsen *et al.* ("The Asian tsunami: a protective role for coastal vegetation," Brevia, 28 Oct., p. 643). Their conclusions confirm assumptions made earlier by Pearce (*1*), Williams (*2*), and many others. Although the authors used a limited analytical approach on a single Indian lagoon, there are some caveats they did not address.

First, the authors assessed pre-tsunami vegetation cover using remotely sensed data and categorized vegetation as dense, open, and no trees. However, as highlighted by Dahdouh-Guebas *et al.* (*3*), "cryptic ecological degradation" in the field may be masked on remotely sensed imagery, and mangroves that appear healthy by species composition and density on remote sensing imagery may in fact be subject to strong qualitative degradation. The concept of cryptic ecological degradation in mangrove forests is even more important in light of these forests having provided less protection during the recent tsunami than 24 other Sri Lankan lagoons, as evident from cluster analyses (*4*). Considering the ability to extract such important qualitative information at a resolution of species and even individuals (*5*), the very high resolution IKONOS and QuickBird satellite imagery, to which the authors had access, has not been used to its full potential.

Second, the authors do not identify variation in house construction or variation in mangrove settings as possible factors influencing damage to the villages. The image of the mosque as the only building left standing in Banda Aceh after the tsunami hit (*6*) suggests that the architecture of buildings or the materials that are used for their construction may have been a determining factor in withstanding the tsunami wave. Their fig. 1 suggests that there are at least two different types of mangrove settings: fringing forests and riverine forests (*7*). This may have influenced the impact of the tsunami as well.

Finally, only three of the villages analyzed are located behind a potential barrier. Most of the villages were very close to the ocean (see Danielsen *et al.*'s fig. 1), in which tsunami destruction, somehow attenuated by beachfront *Casuarina* plantations, is evident. A comparison between villages located at a (similar) distance from the coastline but protected to various extents by different types of barriers or no barriers at all is not made. Such a comparison could have accounted for the variation in distance to the coast.

FARID DAHDOUH-GUEBAS AND NICO KOEDAM

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Response

WE AGREE WITH DAHDOUH-GUEBAS AND KOEDAM on the need for better understanding of the tsunami mangrove shield. However, we believe the relatively homogenous coastal characteristics of our study site minimized intrasite differences in the energy of the incoming tsunami and allowed the benefits of a tsunami tree shield to be studied.

The few (*1*) field-based and quantitative studies of the shielding function of mangroves against wind-induced waves (*2*, *3*) cannot be generalized to tsunamis. The hydraulic resistance of mangroves to tidal flow (*4*, *5*) differs substantially from their resistance to wind-induced waves (*3*), suggesting that the protective capacity of mangroves varies according to the time scale of the waves (*6*). Tsunami waves have a period of 1 to 2 hours (*7*), compared with wind-induced waves (<20 s) and tidal flow (diurnal and semidiurnal). As tsunami waves behave differently from other waves (*8*), their hydraulic properties cannot be estimated by interpolation.

Analysis of QuickBird (0.6-m pansharpened pre-tsunami) and IKONOS (4-m multispectral post-tsunami) images and ground surveys by scientists with 13 years of experience in the study area demonstrated quantitatively

Tsunami-stricken areas near the coastal outskirts of Banda Aceh, Indonesia, on 27 December 2004.

CREDIT: AP PHOTO/XINHUA, ENWAER

(see our table S1) (*9*) the benefit of the tsunami tree shield. Assessing the impact of mangrove condition in modifying relative protection would require analysis of matched pairs of pre- and post-tsunami 0.6-m QuickBird or 1-m IKONOS images, which were not available. Field surveys indicated, however, that forest condition was relatively uniform.

Variations in house construction and physiognomy of the mangroves are potential caveats. Across the study area, there were no significant differences in house construction, but variations in the physiognomy of mangroves require further study.

Unprotected villages in the northern portion of the study site were compared with villages partly protected by *Casuarina* in the south, but no villages with and without mangroves were equidistant from the coast. Despite this analytical weakness, our results and data from Sri Lanka (*10*) suggest that by maintaining or planting coastal forests, humans enhance protection of coastal areas against tsunamis. Observations of tropical cyclone impact (*11*) further suggest the need for a coordinated strategy (*12*) to maintain or restore coastal wetlands, forests, or sand dunes—especially along vulnerable tropical and subtropical coastlines. Such a strategy would not only provide protection against tsunamis but also mitigate the impacts of storms and sea level rise (*13*).

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Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

TECHNICAL COMMENT ABSTRACTS

Comment on "A Hydrogen-Rich Early Earth Atmosphere"

David C. Catling

Tian *et al.* (Reports, 13 May 2005, p. 1014) proposed a hydrogen-rich early atmosphere with slow hydrogen escape from a cold thermosphere. However, their model neglects the ultraviolet absorption of all gases other than H_2. The model also neglects Earth's magnetic field, which affects the temperature and density of ions and promotes nonthermal escape of neutral hydrogen.

Full text at www.sciencemag.org/cgi/content/full/311/5757/38a

Response to Comment on "A Hydrogen-Rich Early Earth Atmosphere"

Feng Tian, Owen B. Toon, Alexander A. Pavlov

Catling speculates that the exobase of early Earth was hot and that the ancient nonthermal escape rate was more than 1000 times the present rate. However, low oxygen and high carbon dioxide on early Earth yields a cold exobase, and nonthermal escape rates are limited and cannot balance the volcanic outgassing of hydrogen.

Full text at www.sciencemag.org/cgi/content/full/311/5757/38b

APPLIED PHYSICS

Steps to the Light Fantastic

Colin Webb

Jeff Hecht, the author of several books and a correspondent for *New Scientist*, has been writing about lasers and optics for three decades. In his latest book, he documents the twists and turns along the path that led to the demonstration of the first working laser. The race he describes in *Beam* all happened in a short span of time—most of the action took place between 1957 and 1961.

In 1954, Charles Townes and his students at Columbia University, working at microwave frequencies using the MASER (microwave amplification by stimulated emission of radiation) concept, showed how the process of stimulated emission could be harnessed to make powerful oscillators and amplifiers. The idea of extending the range of operation to the much higher frequencies of visible light to make an "optical maser" or "laser" was clearly an attractive one, but as late as 1957 two obstacles barred the way. The first was the identification of a suitable amplifying medium—one in which more atoms populated the upper rather than the lower of two energy levels connected by an optical transition. The second was the problem of how to make a cavity that would act as a resonator at optical wavelengths. For microwaves, this had meant constructing a six-sided reflective box a few wavelengths across, but at optical wavelengths such a minute cavity looked totally impractical.

In late 1957, the solution to the resonator problem occurred to Gordon Gould, then a graduate student working at Columbia (with Polykarp Kusch as his thesis adviser). Gould foresaw that two highly reflective mirrors, accurately aligned to be exactly parallel, could form an optical resonator even if they were separated by many hundreds of thousands of optical wavelengths. Gould had his workbook entries (*1*) notarized and duly applied for a patent covering this and many other ideas for making a practical optical maser, which he referred to as a "laser." Quite independently, the same idea occurred to Arthur Schawlow, Townes's brother-in-law, in early 1958. Schawlow was a scientist working at Bell Laboratories, where Townes held a consultancy. The two wrote up their proposal for "infrared and optical masers" in a landmark paper published in December 1958 (*2*).

With a solution to the resonator problem in view, the race was on to find a medium that could provide optical gain. In early 1959, three approaches were being pursued: At Bell Labs in New Jersey, Schawlow was looking for a solid-state solution, while Ali Javan, William Bennett Jr., and Donald Herriott were studying the spectroscopy of neon in the hope that discharges in neon gas might show gain. And Gould—who in the meantime had given up his Ph.D. studies and joined a small research company (TRG), whose management he persuaded to back his ideas—had submitted a proposal to the U.S. military for a classified research project based on optically pumped alkali metal vapor as the gain medium.

Productive ruby. Theodore Maiman and Irnee D'Haenens display the first laser, 25 years after they made it.

CREDIT: HUGHES RESEARCH LABORATORY PHOTOGRAPH/COURTESY EMILIO SERGE VISUAL ARCHIVES, AIP

Hecht's book goes on to relate how in September 1959, at an international symposium on "quantum electronics-resonance phenomena" held in the Catskills, it became evident that there were yet more runners in the race. A Soviet delegation included the famous Alexander Prokhorov and Nikolai Basov, whose 1955 paper (*3*) had disclosed how far their work on microwave masers had progressed. Also present were Peter Sorokin and Mirek Stevenson from IBM Laboratories and Theodore Maiman, a researcher from the Hughes Research Laboratories in Malibu, California. Microwave masers were the topic of most of the papers presented, and of the two concerning lasers, that by Schawlow poured cold water on the prospect that ruby might be suitable as an amplifying medium.

Beam
The Race to Make the Laser

by Jeff Hecht

Oxford University Press, New York, 2005. 284 pp. $29.95, £18.50. ISBN 0-19-514210-1.

The first to pass (in May 1960) the winning post was a dark horse in more than one sense. Despite the resources that Bell Labs could bring to bear and the Pentagon money backing TRG, it was Maiman who triumphed—and he did so using the very material (pink ruby) upon which Schawlow had cast considerable doubt (*4*). There was of course a twist. While Schawlow, along with the rest of the world, had been thinking in terms of a continuously working laser, Maiman's device used pulsed excitation from a xenon flashlamp. Ironically, Maiman was denied swift publication in a premier journal by the failure of the editor of *Physical Review Letters* to recognize the first demonstration of a working laser as the great advance it undoubtedly was.

Sorokin and Stevenson at IBM got their pulsed laser (which used uranium-doped calcium fluoride) working in November of 1960 (*5*). To avoid the problem of misunderstanding its significance, they delivered their manuscript to the editor of *Physical Review Letters* in person. However, Maiman's frustration over delays in the publication of his claim pales into insignificance when compared to the difficulties faced by Gould at TRG. Gould's earlier flirtation with communism prevented him from gaining the necessary clearance to work on the project that he himself had originated, so he had to stand back and let others do the work that interested him. Eventually, in March 1962, his TRG colleagues Paul Rabinowitz and Steve Jacobs succeeded in obtaining oscillation in optically pumped cesium vapor (*6*). But the honors for achieving the first truly continuous laser action belong to the Bell Labs team, which achieved laser action in helium-neon discharges late in December 1960 (*7*).

Hecht's narrative presumes no specialist knowledge of the science on the part of the reader—indeed there are no equations in the book. It is a history based on first-hand interviews with most of the scientists who participated in these discoveries, accompanied by fully documented sources and a useful bibliography. Hecht attempts, and I think succeeds, in distributing the credit fairly among those involved. Future historians of science will certainly find *Beam* a valuable resource. General readers can enjoy it as a readable account of how science is actually done.

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PHYSICS

Bringing Hidden Dimensions into View

James D. Wells

A scientific revolution is in the making. Particle detectors, electrical wire, magnets, and people are coming in sealed trains to Geneva, Switzerland, for the planned 2007 start of the Large Hadron Collider at the European Laboratory for Particle Physics (CERN). Experimental physicists are writing computer programs, testing equipment, and arranging housing. They await the collision of protons at extraordinarily high energies—higher than humans have ever achieved before. They are curious. They know from mathematical analysis that something new must develop beyond what we know today, otherwise scattering probabilities among known particles at these high energies will be nonsensical. But what precisely will happen? Although no one knows for sure, experiments should tell.

Theoretical physicists await the experiments with equal anticipation. In preparation for this revolution, some theorists calculate the predictions of standard-model particle interactions at ever higher precision in order to compare them with the new experiments. "Standard model" is the lackluster title given to the sum of current particle physics knowledge, which includes the properties of known elementary particles (electrons, quarks, etc.) and the forces that determine their interactions.

Warped Passages
Unraveling the Mysteries of the Universe's Hidden Dimensions / Unravelling the Universe's Hidden Dimensions

by Lisa Randall

Ecco, New York, 2005. 512 pp. $27.95, C$37.95. ISBN 0-06-053108-8. / Allen Lane, London. £25, C$40. ISBN 0-713-99699-4.

Other theorists speculate on what the high-energy frontier has in store for us. They identify problems with our current understanding of the basic laws of nature and posit solutions for those problems. Lisa Randall, a professor of physics at Harvard, is among the very top of these theorists. It is a treat for readers at all levels to have one of the leading experts write a book about what she's been up to. In *Warped Passages*, Randall does not disappoint.

The book's main focus—the source of its title and what will surely stay with its readers the longest—is not so much the important problem in physics that Randall addresses but rather her proposed solution. In this case, the solution is the hypothesized existence of extra dimensions of space. These dimensions are not your parents' dimensions. They are tiny and warped. Their existence is not intuitive, and Randall explores nearly every possible way to explain the idea, employing everything from a garden hose to classic children's literature in this pursuit. Most of the connections she makes are clever and work well.

Why extra dimensions? An idea gains respect only when it holds promise of solving an important problem. In this case, the extra warped dimensions may solve the hierarchy problem: Why is the scale of known elementary particles (i.e., their masses and interaction strengths) so different from the scale of Newton's gravitational constant?

Within the particle physics community, there is almost universal acceptance of the severity of the hierarchy problem. All the arguments come in the hypothesized explanations. Most theoretical explanations for the problem have been killed off by additional unwanted predictions. A particularly difficult iatrogenic illness is the prevalence of one type of particle (say, a muon) decaying into another type of particle (electron) more often than experiment says is allowed. And since experiment is axiomatic to all good physicists, the offending theories are put to rest quickly. There are no obvious showstoppers of this sort in Randall's theory, which is remarkable given the radical nature of the idea.

The particle physics community has a long history of exploring the various interesting properties of extra dimensions, stretching back to at least the 1920s. Albert Einstein is just one of the many illustrious physicists who have been enamored with the idea. The modern frenzy grew out of a 1998 paper by Nima Arkani-Hamed, Savas Dimopoulos, and Gia Dvali, who showed that invoking extra dimensions enabled recasting the hierarchy problem, from one of quantum corrections of particle masses to that of geometry of extra-dimensional space (*1*). Any new ways to attack the hierarchy problem are always welcome, and their clever insights set many theorists scrambling to go deeper.

One difficulty is that the geometry problem started to look just as intractable as the old problems. A year later, in a pair of remarkable papers (*2*, *3*), Randall and her collaborator Raman Sundrum showed that the geometry problems of warped extra dimensions, as opposed to standard or "flat" extra dimensions, are not as problematic. Soon after, Walter Goldberger and Mark Wise showed that the warped extra dimensions could be stabilized by natural particle physics models (*4*). Randall beautifully describes this theoretical odyssey, emphasizing the physics but also sprinkling it with a personal touch.

Of course, with new ideas come new questions and challenges, and the Randall-Sundrum approach is no exception. For example, many theorists wonder how this approach can tune the cosmological constant (a background energy density permeating the universe) to the tiny value observed by experiment. That is a fair criticism, but not necessarily lethal. The Randall-Sundrum idea may well overcome all objections based on cosmological constant arguments once people understand better what the true issues are regarding that notoriously difficult problem. In any case, if Randall's ideas are relevant to the hierarchy problem, there is a good chance of finding evidence for it at the Large Hadron Collider.

The main competitor to extra dimensions—one probably having more adherents and practitioners—is supersymmetry. That theory posits that for each particle there is a superpartner. The pair work together to tame quantum corrections of particle masses and thus stabilize the hierarchy of scales. If it has direct relevance to the hierarchy problem, supersymmetry will also be tested experimentally at the Large Hadron Collider. To make things even more interesting, Randall explains why supersymmetry and warped extra dimensions are not mutually exclusive hypotheses, which creates the possibility that both radical ideas could be protagonists in the hierarchy story.

Randall likes to emphasize that her theories are testable. It is a high achievement for a theoretical physicist to tackle a hard problem, come up with an ingenious solution, and realize that it is testable beyond ex post facto predictions within a short period of time. *Warped Passages* recounts such an achievement. Experiment will cast its supreme judgments shortly.

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RESEARCH FUNDING

Peer Review at NIH

Effective grant review requires both continuity and change.

Toni Scarpa

The National Institutes of Health now has a $28 billion annual budget, with more than 80% going to support outside training and research, including grants to more than 3000 universities, medical schools, and other research institutions in the United States and abroad. These funds are allocated in a competitive process, using peer review by independent scientists to identify proposals with the most scientific merit for possible funding. It is a system revered by many, but it faces clear challenges.

Much has changed since the NIH grants program was established 60 years ago (*1*), when we received 800 grant applications. We now get ~80,000 applications a year. The NIH Center for Scientific Review (CSR) reviews and assigns priorities to two-thirds of these applications, recruiting each year more than 15,000 outside scientific experts in various specialized fields. Our regular reviewers volunteer 1 to 3 months a year to read and to assess applications. They then meet three times a year with other members of their review group to discuss and to score applications.

After an application has been assessed by the CSR-managed study section, CSR sends to the NIH institutes and centers a summary statement containing a score (and, in most cases, a percentile ranking), the peer reviewer's comments, and a résumé of review discussions. In the second level of peer review, advisory councils make funding recommendations on the basis of these summaries, taking into consideration the institute or center's scientific goals and public health needs.

> **"…the NIH application review system must evolve to address … new realities."**

Other nations provide direct funding to their research institutions for researcher salaries and facilities and have relatively smaller grant programs to provide additional funds. Although U.S. researchers are hired and formally paid by their academic institutions and medical schools, they depend on NIH and a few other competitive grants programs to support a large and growing fraction of their salaries and laboratory expenses. A scientist who fails to obtain a grant is now less likely to achieve tenure. A new investigator who does not attract grants will soon be forced to consider another career.

Getting a grant is more difficult now as NIH is no longer seeing rapid budget increases. The percentage of grant applications funded is shrinking, partly as a result of multiple applications from the same individuals and, to a lesser degree, as a result of an increase in the number of researchers submitting applications. What makes this situation particularly difficult is that the business plans of most universities and medical schools assume continued growth.

In addition to increased competition for NIH funds, the scope, pace, and complexity of biomedical research has increased dramatically in recent years, and the needs of the research community have changed significantly. An exciting and innovative idea can quickly become dated, and researchers now have less protected time to write applications, to mentor new investigators, or to serve on peer-review groups. All of these realities have put tremendous pressures on the NIH application review system. Our process must evolve to address these new realities.

Competitive pressures have pushed researchers to submit more conservative applications, and we must find ways to encourage greater risk-taking and innovation and to ensure that our study sections are more receptive to innovative applications. We also must find ways to address the fact that clinical research applications may receive slightly less favorable scores than other applications (*2*).

NIH peer reviews are only as good as the reviewers we are able to recruit, and we must do more to enlist the best reviewers. Although face-to-face meetings of reviewers are the ideal and will continue, we are experimenting with new electronic technologies that permit reviewers to have discussions with greater convenience and to spend less of their precious time in traveling. For example, asynchronous Internet-assisted discussions—secure chat rooms—allow reviewers to "meet" and to comment independently of time as well as place.

The investigator-initiated (R01) grant application may be the world's longest of its type—25 dense pages with unlimited appendices. Producing, reviewing, revising, and re-reviewing them takes an enormous amount of time for applicants and reviewers. We should look into whether these multipage applications and appendices are really useful, or if they are an unnecessary burden on reviewers. The seemingly endless appendices may never be read in full and some may never be read at all.

Finally, many have asked if the present two-tiered, 9-month review process should be shortened so that we can keep pace with the science and be more responsive to our applicants. Our system can be particularly frustrating for those who may need to make only minor revisions, because results from our reviews typically come too late for them to reapply for the next review round.

CSR has taken two steps to speed its review process. As of October 2005, we are posting summary statements of most reviews within 1 month after the study section meeting instead of 2 to 3 months after the meeting.

In February 2006, we will begin a pilot study to cut $1^1/_2$ months from our review process as recommended by a Trans-NIH Committee to Shorten the Review Cycle (*3*). Forty CSR study sections will participate in this pilot, which will speed the reviews of R01 applications submitted by new investigators. Resubmission deadlines will be extended to allow these new investigators to resubmit immediately if only minor revisions are necessary. Specifically, we will: (i) schedule study section meetings up to a month earlier; (ii) provide scientists their study section scores, critiques, and panel discussion summaries within a week after the section meeting; (iii) shave days from the internal steps involved in assigning proposals to study sections; and (iv) extend resubmission deadlines by 3 weeks.

If the pilot succeeds, we will seek to expand it. One major step needed before expansion should be completed by October 2006, when all R01 applications must be submitted electronically. CSR also plans to test knowledge-management software for speeding the referral of applications to the appropriate NIH institute or center and to study sections. We will also seek to use this software to speed assignment of applications to reviewers. In initial tests, this software appears quite promising.

Change can be difficult when so much is at stake, but it is urgently needed. For NIH to meet its mission and for science to advance, we must work together. I encourage anyone with a good idea or suggestion to contact me.

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ECOLOGY

Complexities of Coral Reef Recovery

Restoring an area's natural state can have surprising outcomes. Boosting the number of predatory fish in a protected marine reserve has little effect on how well its prey controls seaweed in tropical reefs.

Ove Hoegh-Guldberg

The world's coral reefs are deteriorating—nearly half may have disappeared in the past 30 to 50 years (*1*). The plethora of threats they face include declining water quality, overexploitation, and climate change (*2*). Although there is no single panacea for these problems, marine protected areas have emerged as a potentially powerful means for managing reefs within the world's changing oceans. These protected areas create refugia for species that would otherwise be overfished. Moreover, this may have indirect benefits for the recovery of coral reefs from disturbances such as coral bleaching and outbreaks of crown-of-thorns starfish, which rapidly decrease the abundance of critical organisms such as reef-building corals. Under ideal conditions, marine protected areas should also increase fish stocks in adjacent areas as well, through the movement of species and larvae from the protected areas (*3*).

The science behind marine protected areas is still in its infancy, with few studies having established a firm scientific basis for their impact on fish populations within, and adjacent to, protected regions (*4*). Faced with few other options, however, reef managers have adopted marine protected areas as a major part of their toolkit. Last year, the world's largest marine park, the Great Barrier Reef Marine Park, adopted rezoning in which no-take areas (where fishing is totally forbidden) jumped from 4.6 to 33.4%. In a similar way, the urgency of reversing the rapid disappearance of reef resources has driven plans for no-take reserves to be placed across at least 20% of the Northwestern Hawaiian Islands Coral Reef Ecosystem Reserve in the near future. Given the huge size of such park systems, these are big investments. Yet the complete consequences of this kind of rezoning remain unclear.

Parrotfish and seaweed dynamics on a coral reef. (**Top**) Large-bodied grazers of coral reef seaweeds such as the spotlight parrotfish (*Sparisoma viride*) find refuge within marine protected areas where they reduce the cover of seaweed, which may otherwise outcompete corals if allowed to go ungrazed. (**Bottom**) Parrotfish may consume up to four times as much benthic seaweed inside protected marine areas as they do outside such reserves, using their large beaklike mouths. Parrotfish are preyed upon by species such as the Nassau grouper on Caribbean coral reefs.

Without a firm scientific basis, it is unlikely that protected areas will be optimally designed and integrated with other fisheries management tools or will be able to deliver the high expectations of reef management (*3*). The latter is especially important if marine protected areas are to have any chance of navigating the complex social and political pathway to their adoption by countries that often have few resources to respond to threats facing their reef systems. Given the many gaps in our knowledge about how protected areas work, reef managers often have a hard time convincing reef users and fishers as to why such areas should be implemented.

Coral reefs are complex, and it can be difficult to predict how marine protected areas will influence the processes structuring these ecosystems. One of the first studies to take a critical look at the impact of protected areas on ecosystem processes appears on page 98 of this week's issue. Here, Mumby *et al*. (*5*) have focused on the effect of long-standing marine protected areas in the Bahamas Archipelago and have come up with some intriguing insights into the complex interplay among reserves, predators, and prey. The Exuma Cays Land and Sea Park (456 km^2) encompasses a large and effective protected area that was established 46 years ago and has not been fished since 1986. Mumby's team used a nested analysis that allowed them to infer the effect of reserves on predatory fish biomass and on populations of their prey. In particular, Mumby *et al*. sought to answer the question of whether implementing a marine protected area might have a long-term detrimental impact on the level of grazing, which is primarily carried out by parrotfish on benthic microalgae and seaweeds. By facilitating a recovery of top predators in this ecosystem (*5*), the level of predation on parrotfish (see the figure) could consequently increase. This may not be problematic in a fully natural ecosystem, but with the continued scarcity of the key grazing sea urchin *Diadema antillarum* in the Caribbean (*6*), a reduction in parrotfish could help seaweeds to bloom, thereby placing greater strain on reef-building corals that compete with seaweeds for space on tropical reefs.

The results of Mumby *et al*. illustrate some of the complexity of how marine protected areas might influence coral reef ecosystems. Although increases in predation reduced the size and grazing of some smaller species of parrotfish, the effect was relatively small, decreasing grazing only by 4 to 8%. This is explained by the fact that some of the larger bodied species of parrotfish are just big enough to exceed the mouth size of

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predators (Nassau grouper), and it is these larger parrotfish that do most of the grazing (see the figure). In fact, the protection of larger parrotfish from fishing offered by marine protected areas clearly resulted in a greater biomass of these species within such areas. This enhancement of large-bodied parrotfish within reserves was associated with a net doubling of grazing activity within reserves. This, in turn, led to a factor of 4 reduction in the abundance of seaweed on reefs within the protected areas as opposed to comparable but unprotected areas within the Bahamas Archipelago.

Mumby *et al*. conclude that marine protected areas in the Caribbean will almost always increase the level of grazing within their boundaries, despite increases in predation. The complexity they have uncovered, however, just scratches the surface of what is required to understand the functioning of protected regions. Further studies are needed to ascertain the impact of increased grazing and reduced seaweed cover on the population dynamics of corals and other key organisms. At the same time, parallel studies are needed to understand how impacts resulting from phenomena such as coral bleaching and disease drive changes within benthic communities. This will provide a balanced perspective of the impact of reserves in light of many sources of disturbance. Targeting information gaps on the impact of marine protected areas on key ecosystem processes is a priority if we are to improve the success and use of this potentially important management tool. These requirements also include the need for social and legal frameworks that allow for reserve management to adapt and change as our understanding of these management systems continues to evolve. Although these are substantial challenges, the breathtaking beauty of coral reefs and their importance to tropical coastlines and people makes their pursuit worthwhile.

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PALEONTOLOGY

A Different Kind of Croc

James M. Clark

A fossil crocodilian from Argentina broadens the diversity of marine reptiles. Its remarkably large head and serrated teeth suggest a very unusual kind of creature.

Crocodilians and birds are each other's closest living relative, so the evolutionary lineages leading to each group must have been on Earth an equal amount of time, at least since the Middle Triassic (227 to 242 million years ago). Birds and their extinct relatives the dinosaurs and pterosaurs constitute one of the most diverse vertebrate groups by any measure, but the journey from the common bird-crocodilian ancestor to living crocodilians has not been as uneventful as the 23 living species might suggest. Much of the extinct diversity along the crocodilian lineage was among land-living animals, such as those that developed mammal-like teeth and chewed their food (*1*) and those that held their long slender limbs beneath them like mammals (*2*), but one group—thalattosuchians—joined ichthyosaurs and plesiosaurs in the oceans and seaways of the Jurassic and Early Cretaceous. On page 70 of this issue, Gasparini *et al*. (*3*) report a fossil from the Andean foothills of Argentina that reminds us once again not to underestimate the crocodilians of the past.

Thalattosuchians include two groups: the relatively unspecialized teleosaurids and the metriorhynchids, or geosaurs, which became highly adapted to a life-style in the oceans. Whereas teleosaurids probably looked much like a living false gharial (*Tomistoma*), geosaurs had a highly streamlined skull, large paddlelike limbs, smooth skin lacking bony plates, and a downturned tail skeleton like that of ichthyosaurs that was probably complemented by a fleshy upper lobe. Geosaur skulls were similar to those of mosasaurs, giant extinct lizard relatives, which may have replaced them ecologically in the middle of the Cretaceous.

Dakosaurus andiniensis was named in 1996 for a specimen first described in 1987, but it was represented only by a few scraps of bone and teeth. The teeth, with tiny serrations like those on the edge of a steak knife, pointed to affinities with the European *Dakosaurus maximus*, first described in 1858, which was the only known marine crocodilian with serrated teeth. When two skulls of the Andean species were discovered recently—one from the latest Jurassic and one from the earliest Cretaceous—they revealed not a low, streamlined skull like that of other metriorhynchids but a short, high one like that of land crocodilians. In addition to those of *D. maximus*, serrated teeth had been known in several extinct terrestrial crocodilian relatives, such as *Sebecus* and *Baurusuchus*, but the teeth of *D. andiniensis* are more massive than any of these.

Living crocodilians use their mouths to both capture and eat their prey, and there is a

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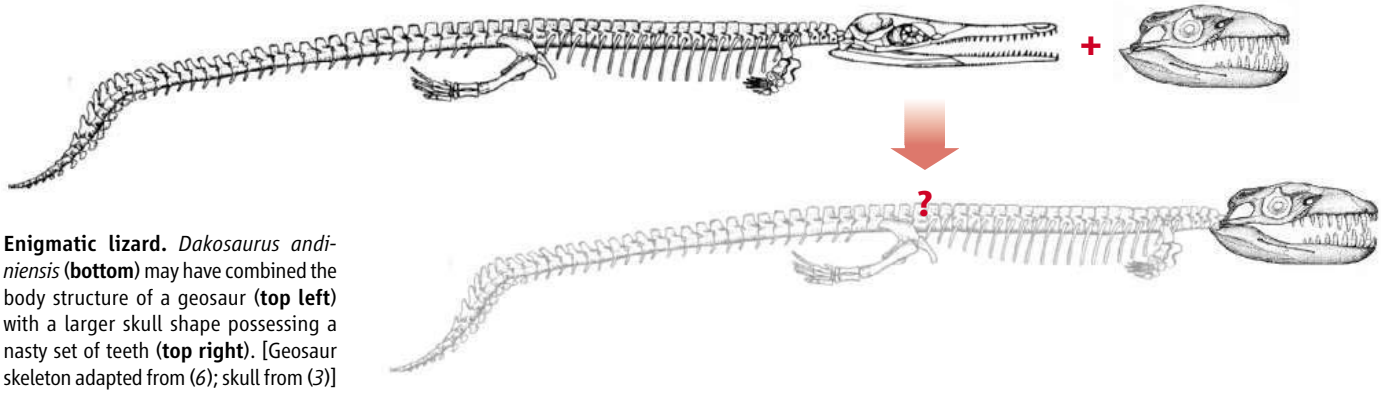

Enigmatic lizard. *Dakosaurus andiniensis* (**bottom**) may have combined the body structure of a geosaur (**top left**) with a larger skull shape possessing a nasty set of teeth (**top right**). [Geosaur skeleton adapted from (*6*); skull from (*3*)]

general correlation between the shape of the skull and the most common prey items (*4*). Most thalattosuchians have a long, low snout with many conical teeth, which by comparison with the living gharial and false gharial suggests a diet predominately of fish or other swimming animals. In this case, the low skull profile allows for swift lateral movement of the head underwater to capture prey, and the long snout with many teeth maximizes the area swept for prey. The tall skull of *D. andiniensis* is an enigma (see the figure), because metriorhynchids have bodies highly adapted to swimming yet here is a skull that is not streamlined and would be difficult to move side-to-side through the water. Furthermore, it has reduced the number of teeth, increased their size, and added serrated edges to them, unlike fish-eating forms but like terrestrial carnivores. The great height of the skull may be due to the space requirements of the roots of its large, uncurved teeth in the maxilla bone, but this doesn't help to understand how it was using its head to capture prey.

So how did *D. andiniensis* use its head to capture prey? The shape of the head suggests that, unlike the head of living crocodilians, it was not used to grab and hold prey and then twist it in the water. The skull of living crocodilians is generally low and wide, and along with the strength provided by its bony secondary palate, this shape conveys great resistance to torsional stresses (*5*). Higher skulls are weaker in this regard, but the greater verticality of the muscles used to close the jaws provides greater power for slashing at prey than in living crocodilians, in which these muscles have a more horizontal orientation. For example, the Komodo monitor lizard has a somewhat similar tall head shape and serrated teeth, with which it slashes at prey and then retracts the head, but whether this feeding strategy could work in a pelagic animal is open to question.

This is where we reach the limits of our current data. Until we have evidence such as stomach contents, coprolites, or tooth marks on prey traceable to *D. andiniensis*, all we can do is speculate about how it used its remarkable head. Indeed, its body skeleton may prove to be just as unusual once it is better known. In any case, there is a new addition to the Mesozoic marine reptile menagerie, one that was surely doing something unpleasant with its head.

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ASTRONOMY

Triangulating the Galaxy

Measurements of a maser in the Milky Way allow precise determination of astronomical distances and should improve estimates of the fraction of dark matter in the galaxy.

James J. Binney

Astronomers can make physical sense of the heavens only if they know the distances to objects, so any advance in distance measurement is important. On page 54 of this issue, Xu *et al.* (*1*) report observations of cosmic methanol maser emissions that resolve a factor of 2 uncertainty in the distance to an object that lies 2 kpc (about 6000 light years) from us. As a result of the measurement, the authors have also shown that this object is moving in the galactic plane, as expected, but at a speed that suggests that the local spiral structure has an impressively large amplitude. This measurement will constrain the fraction of the local galactic density that can come from dark matter.

A better galactic ruler. (**Left**) Schematic of a parallax measurement. This image of M83 shows a spiral galaxy similar to the Milky Way. The distance to an object in a spiral arm can be determined by triangulation measurements from two points on Earth's orbit around the Sun (triangle, not to scale). (**Right**) Image taken by the Spitzer Space Telescope of the W3OH star-forming region in the Perseus arm of the Milky Way that contains methanol maser sources observed by Xu *et al.*

Ultimately all astronomical distances depend on triangulation: We measure two angles in a triangle formed by lines of sight to an astronomical object from two points of known separation. The motion of Earth about the Sun provides a useful separation vector, and the difference between the two angles can be determined with exquisite precision by measuring the slight shift with the seasons in the angle on the sky between the object and an extremely distant object (see the figure). This shift is called the parallax of the source and is inversely proportional to the source's distance.

In the late 1990s, the European Space Agency's Hipparcos satellite revolutionized parallax measurements by determining the parallaxes of several thousand stars to a precision of about one milli–arc second (mas), equivalent to 5×10^{-9} radian, which is sufficient to obtain reliable distances for objects closer than about 100 pc. Xu *et al.* used radio interferometry to determine the parallax of an object to within 0.01 mas, which enables reliable distances to be determined for objects

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closer than 10 kpc, slightly in excess of the distance to the galactic center. They can obtain this precision because the elements of their interferometer are on different continents, which in turn is made possible by the enormous surface brightness of many maser sources.

The successor to Hipparcos, Gaia, is scheduled to be launched in late 2011, and by 2015 it will be yielding parallaxes of comparable precision for tens of millions of stars. Unfortunately, Gaia will work only at optical wavelengths, with the consequence that much of the galactic plane and center will be hidden from it by dust. Radio-frequency observations of masers are not hindered by dust, so even a decade from now the technique demonstrated by Xu *et al.* will be important.

The masers observed by Xu *et al*. lie in a star-forming region called W3OH in the nearby Perseus spiral arm of the Milky Way. Doppler measurements of the line-of-sight velocity of this region, together with the assumption that it is on a circular orbit around the galactic center, yield a distance of 4.2 kpc (*2*), nearly twice as great as the distance estimated from the brightness of some of the region's stars (2.2 kpc). Xu *et al.* find the distance to be 1.95 kpc and thus demonstrate that the region is not on a circular orbit. The results of Xu *et al*. complement the known line-of-sight velocity with the velocity on the plane of the sky, and they show that W3OH is moving in the galactic plane at about 22 km s^{-1} with respect to the circular orbit through its location. This velocity differential is larger than the velocity dispersion of star-forming clouds by a factor of 3 to 4. W3OH probably acquired its large peculiar velocity by falling into the spiral arm's gravitational potential. For this to be the case, a substantial fraction of the Galaxy's mass would have to be concentrated in the disk rather than the dark halo, and the arm-interarm density contrast of the Galaxy's spiral pattern would have to be at the upper end of the anticipated range.

When the first clear near-infrared images of spiral galaxies were made about a decade ago, astronomers were surprised by the large amplitudes of the spirals seen in them (*3*). Given that near-infrared luminosity is dominated by stars that together contain most of the disk's mass, this finding implied that spiral structure is associated with density fluctuations. The results of Xu *et al.* are consistent with this picture. Modeling of gravitational microlensing and noncircular motions inside the solar circle has demonstrated that at most a small fraction of the matter in the inner several kiloparsecs of the Galaxy can be in exotic dark matter rather than stars (*4*, *5*). The distance from the galactic center to W3OH is 1.2 times the distance to the Sun, so if the Xu *et al*. datum could be complemented by similar measurements of noncircular motions outside the solar circle, the same argument could be used to constrain dark matter's contribution to the mass budget outside the solar circle, where it is thought to be dominant.

Xu *et al*. have opened up a new era of trigonometric parallaxes by exploiting the enormous surface brightnesses of maser sources. They show that distances can now be determined geometrically to sources that lie within a sphere that extends to beyond the galactic center. The next decade will see a trickle of such measurements that will become a flood around 2015 after Gaia has flown. These measurements will have a big impact on our understanding of what galaxies are and how they work.

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NEUROSCIENCE

A New Molecule to Brighten the Mood

Depression has long been linked to a defect in signals elicited by the neurotransmitter serotonin. This may be due to a deficit of a key protein in the brain that makes receptors for serotonin available for action.

Trevor Sharp

Depression is a mood continuum, ranging from normal but temporary "bad days" to a completely disabling clinical condition characterized by overwhelming despair that lasts for weeks or months. A popular theory is that a breakdown in signaling by the brain neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) is critically involved in the symptoms of clinical depression, but the nature of this defect has proved elusive. The study by Svenningsson *et al*. on page 77 of this issue (*1*) identifies a powerful interaction between a brain protein called p11 and a serotonin receptor (5-HT_{1B} subtype) that has been previously associated with mood regulation. Moreover, in a clever set of experiments using human brain and sophisticated animal models, the authors show that a deficit of p11 is linked to depression, whereas an increase in p11 is linked to the relief of depression. Overall, this finding represents compelling evidence that p11 has a pivotal role in both the cause of depression and perhaps its successful treatment.

The 5-HT_{1B} receptor is one of 14 serotonin receptor subtypes and is abundant in the brain across a range of species (*2*). The rodent 5-HT_{1B} receptor is well suited for investigation because it is remarkably similar in structure, functional characteristics, and distribution to the human homolog. Recent studies using newly available ligands for the 5-HT_{1B} receptor and genetically altered mice with the 5-HT_{1B} receptor "knocked out" have firmly linked this receptor to an extraordinarily diverse range of physiological functions and behaviors including not only mood but also cognition, aggression, addiction, sleep, and feeding (*3*).

To produce this range of effects, the 5-HT_{1B} receptor must be transported to the terminal membranes of both serotonin- and nonserotonin-containing neurons, where it signals by coupling to intracellular heterotrimeric GTP-binding proteins (G proteins). Unraveling this trafficking process presents a major challenge, however, because recent discoveries for other G protein–coupled receptors suggest the involvement of complex networks of interacting proteins, which may number several dozen (*4*).

Using yeast two-hybrid screening, Svenningsson *et al*. identify p11 as the first known protein-binding partner of the 5-HT_{1B} receptor. p11, which is a member of the S100 family of proteins that translocate their binding partners to the plasma membrane (*5*), was shown to have a distribution in the mouse brain that overlaps that of the 5-HT_{1B} receptor. Using simple cell culture systems, Svenningsson *et al*. convincingly show that p11 makes more 5-HT_{1B} receptors available at the cell surface, thereby increasing 5-HT_{1B} receptor signaling efficacy, while leaving the dynamics of other G protein–coupled receptors unchanged. The discovery of p11 now invites investigation of the myriad other interacting proteins that are likely to be critical to 5-HT_{1B} receptor function.

Interestingly, Svenningsson *et al*. found decreased p11 expression in postmortem brains of depressed patients, and also in a well-validated genetic mouse model that displays many

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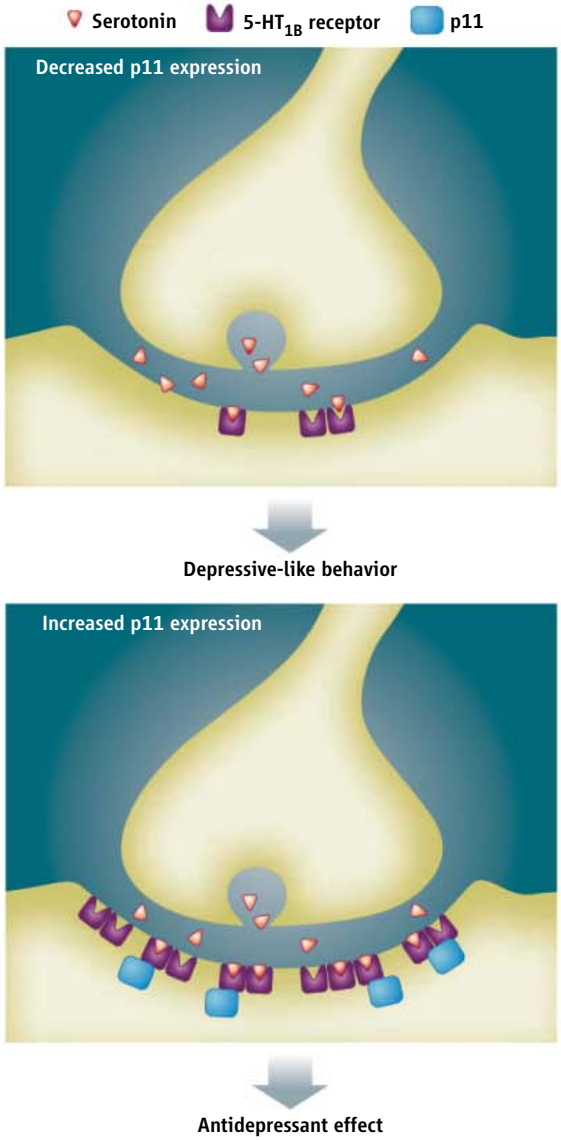
of the behavioral and physiological symptoms of clinical depression (*6*). Crucially, p11 knockout mice exhibited increased depression-like behavior, whereas genetically altered mice that overexpress p11 showed the opposite behavior. These observations provide a convincing association between p11 expression and depression-like behaviors in animals (see the figure), and suggest that a deficit in p11 expression is linked to depressive illness in patients. If the postmortem p11 data are replicated in larger populations of depressed patients, this would be a major breakthrough in our molecular and genetic understanding of depression.

What might cause a deficit in p11 expression in depression? Evidence that other serotonin-related gene products (including tryptophan hydroxylase, 5-HT_{1A} receptors, and the serotonin transporter) are abnormal in depression (*7*) suggests that a generalized dysfunction of serotonin neurons, possibly of developmental origin, may be responsible. However, the different anatomical localizations of some of these gene products might argue for more than one underlying pathophysiological mechanism. On the other hand, depression is often associated with stressful life events and an ensuing excess of glucocorticoid hormones, which can have striking effects on the serotonin system at many levels (*8*). Because the expression of p11 and other members of the S100 family is sensitive to glucocorticoids (*9*), stress may be a factor in the p11 changes.



Mood may be linked to changes in the brain protein p11. p11 increases trafficking of the serotonin 5-HT_{1B} receptor to the neuronal plasma membrane where it can bind to serotonin that is released into the neuronal synapse. Deficits in p11 are associated with increased depressive-like behavior (**top**), and increases in p11 can be linked to antidepressant effects (**bottom**). For clarity, the localization of 5-HT_{1B} receptors on serotonin-containing neurons is not shown.

The past decade has seen the evolution of a fascinating theory to explain the antidepressant effect of drugs like Prozac that act to inhibit the reuptake of serotonin by neurons. This theory posits that elevated serotonin levels trigger signaling cascades that activate gene programs to enhance neuronal survival and connectivity—the latter having failed because of the adverse effects of stress and other environmental factors (*10*). Although this line of thought is driving promising pharmacological strategies for improved antidepressant therapies, our knowledge of the key molecules that are changed by antidepressants to bring about the relief of the symptoms of depression is far from complete.

Intriguingly, Svenningsson *et al.* found that administration of different antidepressants to mice increased p11 expression. In addition, antidepressant-induced behavioral effects in mice were replicated by p11 overexpression and attenuated by genetic removal of p11. These observations pinpoint increased p11 expression as a crucial event in the cascade of molecular changes leading up to the behavioral effects of antidepressant treatment.

Because of the strong p11–5-HT_{1B} receptor interaction, it is tempting to suggest that altered 5-HT_{1B} receptor signaling is the cause of the behavioral changes induced by genetic manipulation of p11 expression. Indeed, Svenningsson *et al*. show that the behavioral effects in mice induced by changes in p11 expression are accompanied by parallel changes in 5-HT_{1B} receptor expression. However, this notion should be interpreted with caution. p11 also mediates trafficking of certain cation channels (*11*, *12*), and changes in this function of p11 might influence mood, although presently this link is tenuous. In addition, unlike p11 deficits, pharmacological or genetic interventions that attenuate 5-HT_{1B} receptor signaling do not evoke overt signs of behavioral depression in animals (*13*, *14*). However, such interventions may not accurately model the effects of p11 deficiency.

Despite these caveats, there is tantalizing evidence of reduced 5-HT_{1B} receptor function in depressed patients (*15*, *16*) that might profit from further investigation. For instance, novel compounds are being developed to image 5-HT_{1B} receptors in living humans (*17*). Moreover, there are reports that triptan drugs with 5-HT_{1B} agonist properties, which are widely used in the treatment of migraine, have antidepressant effects in patients and that more selective agonists with better brain penetrability are antidepressant in animal models (*18*–*20*).

The cause of depression and the relief of its symptoms are likely to be influenced by many different genes. The list of candidate genes linked to the function and effects of serotonin now grows, not just through the addition of p11, but also the large number of serotonin receptor–interacting proteins that p11 represents. The case for p11 as a key molecule in mood regulation is convincing, and it is now timely for translational science to take this exciting development to the next step.

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When Does "Economic Man" Dominate Social Behavior?

Colin F. Camerer[1]* and Ernst Fehr[2,3]†

The canonical model in economics considers people to be rational and self-regarding. However, much evidence challenges this view, raising the question of when "Economic Man" dominates the outcome of social interactions, and when bounded rationality or other-regarding preferences dominate. Here we show that strategic incentives are the key to answering this question. A minority of self-regarding individuals can trigger a "noncooperative" aggregate outcome if their behavior generates incentives for the majority of other-regarding individuals to mimic the minority's behavior. Likewise, a minority of other-regarding individuals can generate a "cooperative" aggregate outcome if their behavior generates incentives for a majority of self-regarding people to behave cooperatively. Similarly, in strategic games, aggregate outcomes can be either far from or close to Nash equilibrium if players with high degrees of strategic thinking mimic or erase the effects of others who do very little strategic thinking. Recently developed theories of other-regarding preferences and bounded rationality explain these findings and provide better predictions of actual aggregate behavior than does traditional economic theory.

Most economic analyses are built on two major simplifying assumptions about human nature: Individuals are assumed to be rational decision makers and to have purely self-regarding preferences. The modeling of complex social phenomena often involves simplifying assumptions like these; otherwise, models may quickly become mathematically intractable. The rationality assumption consists of two components: first, individuals are assumed to form, on average, correct beliefs about events in their environment and about other people's behavior; second, given their beliefs, individuals choose those actions that best satisfy their preferences. If individuals exhibit, however, systematically biased beliefs about external events or other people's behavior or if they systematically deviate from the action that best satisfies their preferences, we speak of bounded rationality. Preferences are considered to be self-regarding if an individual does not care per se for the outcomes and behaviors of other individuals. Self-regarding preferences may, therefore, be considered to be amoral preferences because a self-regarding person neither likes nor dislikes others' outcomes or behaviors as long as they do not affect his or her economic well-being. In contrast, people with other-regarding preferences value per se the outcomes or behaviors of other persons either positively or negatively. A large body of evidence accumulated over the last three decades shows that many people violate the rationality and preference assumptions (*1*, *2*) that are routinely made in economics (*3*). Among other things, people frequently do not form rational beliefs, objectively irrelevant contextual details affect their behavior in systematic ways, they prefer to be treated fairly and resist unfair outcomes, and they do not always choose what seems to be in their best interest.

It seems obvious that these violations of the rationality and preference assumptions will appear in the behavior of aggregate entities like markets and organizations or in political processes. This view is premature, however, because many experiments also indicate that a share of the subjects do not violate the above assumptions and, as we will show, the existence of these subjects may cause aggregate outcomes to be close to the predictions of a model that assumes that everyone is rational and self-regarding. The question is therefore how the interactions among heterogeneous subjects shape the aggregate outcome. The intuition into the processes at work can be sharpened by considering how self-regarding individuals and strong reciprocators (*4*) interact in both sequentially and simultaneously played prisoners' dilemma (PD) games. Recent research has documented the existence of a substantial share of strong reciprocators who exhibit a particular form of other-regarding behavior (*5*). Strong reciprocators show a combination of altruistic rewarding, which is a predisposition to reward others for cooperative, norm-abiding behaviors, and altruistic punishment, which is a propensity to impose sanctions on others for norm violations. Strong reciprocators bear the cost of rewarding or punishing even if they gain no individual economic benefit from their acts (*4*).

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Cooperation in the Presence of Strong Reciprocators

A PD can be illustrated by a situation in which two geographically separated individuals, A and B, have the chance to engage in a mutually beneficial economic exchange. A and B each possess a good that they value, say, at 10, but each player values the other player's good higher, say at 20. Therefore, if the players send their goods to the exchange partner, they both end up with a more highly valued good than if they retain their goods. There would be no problem if the players could sign a contract that an impartial court could enforce. In the absence of such contract-enforcement institutions, however, the situation represents a PD: A is better off keeping his good, irrespective of whether B sends his good to A. Because the situation is symmetric, B faces the same economic incentives and both players will, therefore, forego the opportunity for a mutually beneficial exchange if they are self-regarding. Strong reciprocators, however, are willing to send their good if they know or believe that the exchange partner will also do so. Thus, the exchange may take place in the presence of strong reciprocators. But what happens if a strong reciprocator (say, player B) faces a self-regarding player A and both players know each other's preferences? If the PD is played simultaneously, i.e., if the goods have to be sent off at the same time, no exchange will take place because B anticipates A's decision to retain the good and does likewise. Thus, the existence of the self-regarding player A induces the strong reciprocator B to behave noncooperatively as well. If the exchange is structured sequentially, however, with A sending off his good first, exchange will take place because A knows that B will only send his good if he first receives A's good. Player A knows, therefore, that if he does not send his good first, no exchange will take place; if, instead he sends his good first, B will reciprocate and both players will be better off. It is, therefore, in A's self-interest to send the good in the sequential exchange; the existence of the strong reciprocator induces the self-regarding player to behave cooperatively in this situation.

The existence of strong reciprocators may generate cooperative outcomes most of the time, even if both players are completely self-regarding but have reason to believe that they face a strong reciprocator with positive probability. Suppose, for example, that there are r = 51% reciprocators in the population and 49% self-regarding players. Suppose further that A and B play the sequential PD, say, 10 times

and player A does not know whether B is a strong reciprocator. In this situation it is still rational for a self-regarding player A to cooperate (i.e., send the good) even in the final period as long as he believes that he faces a strong reciprocator with more than a 50% chance. Why? If A defects, he knows for sure that the opponent will also do so (i.e., will not send the good) so that A's payoff is 10. But if A cooperates, his expected payoff is $r \times 20 + (1 - r) \times 0$ if $r > 50\%$. A self-regarding player B therefore has a strong incentive to reciprocate A's cooperation in all but the final period because otherwise B would reveal that he is not a reciprocator and this would induce player A to stop his cooperation immediately. Thus, the mere belief that there are reciprocators generates strong cooperation incentives even among purely self-regarding players to gain a reputation by mimicking the behavior of strong reciprocators. In fact, it has been shown that reputation incentives emerging from the belief that the opponent might be a strong reciprocator (tit-for-tat player) may drive cooperation among purely self-regarding players even in simultaneous cooperation games (*6*) and even if r is very small (*7*, *8*).

Theory also shows that a relatively small minority of strong reciprocators can generate cooperative outcomes in one-shot n-person PD games ($n > 2$) if the players are given an explicit punishment opportunity (*9*). Suppose that after the players in the PD have made their choices, they can punish the other players at a cost to themselves. Self-regarding players will never punish in this situation because the game is one-shot and thus there are no future benefits from current investments into punishment. Strong reciprocators will, however, punish defectors even in one-shot situations, providing strong incentives for the self-regarding players to cooperate. Experimental evidence has shown that this threat of punishment may generate very high cooperation rates in stable groups in situations where self-regarding players alone would reach zero cooperation (*10*, *11*) (Fig. 1). However, in the absence of an explicit punishment opportunity, cooperation converges to very low levels (Fig. 1). In fact, theory shows that even a small minority of self-regarding players suffices to induce a large majority of reciprocators to defect in the simultaneous n-person PD (*9*).

All these examples illustrate an important lesson: Individuals who violate the assumptions of economics may create powerful economic incentives for Economic Man to change his behavior, but depending on the economic structure, the existence of Economic Man may also create strong incentives for those with bounded rationality or other-regarding preferences to behave like Economic Man. This principle not only applies to questions of cooperation but is likely to play a role in many other domains, including behavior in bargaining encounters, in competitive markets, as well as in coordination behavior in organizations or in society at large.

The Effects of Competition in the Presence of Strong Reciprocators

To show how the interactions between strong reciprocators and self-regarding individuals shape bargaining behavior, we consider the ultimatum game (*12*), in which a buyer offers a price p to a seller, who can sell an indivisible good. For simplicity, assume that the buyer values the good at 100 and the seller values it at 0. The buyer can make exactly one offer to the seller, which the latter can accept or reject. Trade takes place only if the seller accepts the offer. If the seller is self-regarding, she accepts even a price of 1 because 1 is better than nothing. Thus, a self-regarding buyer will offer $p = 1$ so that the seller earns almost nothing from the trade. Strong reciprocators reject such unfair offers, however, preferring no trade to trading at an unfair price. In fact, a large share of experimental subjects reject low offers in this game, across a wide variety of different cultures (*13*, *14*), even when facing high monetary stakes (*15*, *16*). This fact induces many self-regarding buyers to make relatively fair offers that strong reciprocators will accept. Often the average offers are around $p = 40$, and between 50% and 70% of the buyers propose offers between $p = 40$ and $p = 50$ (Fig. 2A). The behavior of both buyers and sellers changes dramatically, however, if we introduce just a little bit of competition on the seller's side (*13*, *17*, *18*). Assume, for example, that instead of one there are two sellers who both want to sell their good. Again the buyer can make only one offer which, if accepted by one of the sellers, leads to trade. If both sellers reject, no trade takes place; if both sellers accept, one seller is randomly chosen to sell the good at the offered price. Almost all buyers make much lower offers (Fig. 2A) in this situation, and almost all sellers accept much lower offers (Fig. 2B). In fact, if one introduces five competing sellers into this game, prices and rejection rates converge to very low levels such that the trading seller earns only slightly more than 10% of the available gains from trade (Fig. 2, A and B).

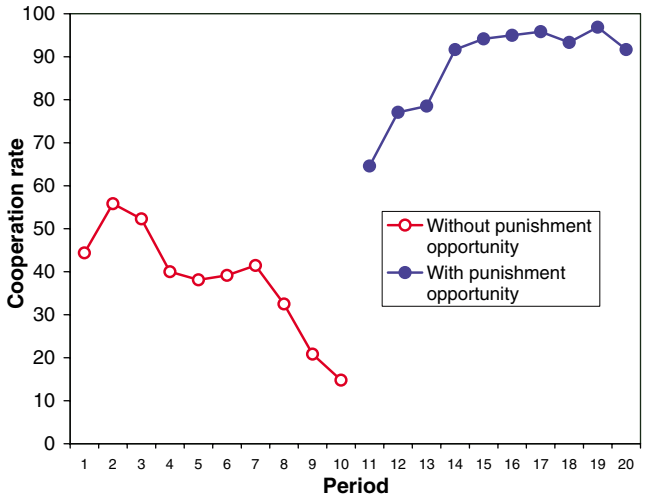

Fig. 1. Cooperation rate in an n-person prisoners' dilemma game with stable groups (*11*). During the first 10 periods, subjects had no opportunity to punish defectors. From period 11 onward, each subject could punish at a cost every other group member after observing their cooperation and defection choices.

Early research on the ultimatum game interpreted the egalitarian outcomes in this game as a sign that people enforce a norm of fairness (*19*). However, if all people obey norms of fairness, why does the price sink to such low levels in the presence of only a little bit of competition among sellers? Heterogeneity in other-regarding preferences is again the key to answering this question, but even if we assume that only a share of the people are strong reciprocators, we still face a puzzle. After all, as Fig. 2, A and B, shows, almost all the experimental subjects make low offers and accept low offers under competitive conditions. Why do fair-minded strong reciprocators, when in the role of a buyer, make such low offers and why do they, when in the role of a seller, accept these low offers? A simple answer to this question would be that competition changes people's preferences; it makes them more selfish. But this would be an uninformative answer; if one can arbitrarily choose the kind of preference that explains an observed behavior, one can explain every behavior and, hence, in fact, nothing. Therefore, the challenge is to explain these facts on the basis of a given distribution of strong reciprocators and selfish subjects (*9*, *17*).

The low rejection rate of reciprocal sellers under competition can be explained if one recognizes their motives. Much research has shown that strongly reciprocal subjects have the goal of punishing unfair behavior or of establishing a fair distribution of outcomes (*2*, *20*). Competition undermines or removes the possibility of meeting these goals in a heterogeneous population of self-regarding and reciprocal sellers. A rational reciprocal seller knows that there is a positive probability that the competing seller(s) will act self-regarding, i.e., will accept any positive offer.

Moreover, the more competing sellers there are, the higher the probability that there will be at least one self-regarding seller. If a competing seller accepts a low offer, the reciprocal seller can no longer punish the buyer by rejecting his offer because the buyer can enforce the low price regardless of the reciprocal seller's behavior. Thus, rejections are futile and, therefore, reciprocal sellers will also accept low offers. Here again we encounter a situation where self-regarding agents induce reciprocal agents to behave like self-regarding agents. (*21*)

Recent models of other-regarding preferences explain the phenomena discussed above very well. These models are based on a taste for reciprocation (*22*–*25*), the desire for equitable outcomes (*9*), a distaste for unequal income shares (*26*), or a concern for helping the least well off and the total payoff of the group (*27*). For example, the theory of inequity aversion (*9*), which assumes a share of people with a desire for equitable outcomes, explains why cooperation fails in the absence of a direct punishment opportunity and why it flourishes when the same players have the opportunity to punish group members. The same approach also accounts for the rather egalitarian outcomes in the ultimatum game, while also explaining the low prices in market games with competition (Fig. 2, A and B). In addition, the model predicts when competition does not remove fair behavior. Assume, for example, that the value of the good is not fixed at 100 but is given by $10q$, where q measures the quality of the good and is determined by the sellers' effort. If the quality of the good is difficult to enforce through legally binding contracts, the seller has some leeway in determining q, which implies that he can reestablish equity by selling a low-quality good to an unfair buyer. Note that this opportunity to reestablish equity is also available in the presence of competing sellers. Thus, if q is difficult to enforce through contracts, a seller with a preference for equity provides an economic incentive even for self-regarding buyers to treat the seller fairly because otherwise the seller provides low quality. Experimental evidence in fact shows that competition has little impact on prices under these circumstances (*28*) because the buyers' price offers are mainly driven by the concern to ensure high quality. This result could not occur if there were only self-regarding sellers.

Bounded Rationality and Strategic Complementarity

A useful pair of concepts for understanding when aggregate behavior is, or is not, consistent with full economic rationality are "strategic substitutability" and "strategic complementarity" (*29*, *30*). In consumer theory, goods are substitutes if they satisfy similar needs such as, for example, chicken and beef. Therefore, higher chicken consumption will, assuming all else is held constant, be associated with lower beef consumption. Goods are complements if having more of one good enhances demand for another (e.g., peanut better and jelly). The intuition behind substitutes and complements can be extended to strategic contexts. Strategies are complements if agents have an incentive to match the strategies of other players. Strategies are substitutes if agents have an incentive to do the opposite of what the other players are doing. For example, if a firm can earn more profit by matching the prices chosen by other firms, then prices are strategic complements. If firms can earn more profit by choosing a low price when other firms choose high prices (and vice versa), then prices are strategic substitutes.

The idea of strategic substitution and complementarity was first developed in studies of firm interactions (*29*, *30*) but extends naturally to the interaction of economic agents with limited and unlimited rationality (*31*, *32*). When economic choices are substitutes, then rational agents have an incentive to behave in the opposite way to that of less-rational agents. Therefore, the rational agents' behavior will counteract the impact of less-rational agents on aggregate behavior. However, when choices are complements, then it pays for rational agents to mimic the behavior of the less-rational agents. Therefore, the rational agents' behavior amplifies the impact of less-rational agents on aggregate behavior. There is, in fact, evidence indicating that under strategic substitutability, a minority of rational individuals may suffice to generate aggregate outcomes that are predicted by a fully rational model (*33*) whereas under strategic complementarity, a small minority of irrational individuals may cause outcomes that are completely at odds with the rational model (*34*).

To see the amplifying influence of bounded rationality, consider a simple game in which many players choose numbers from 0 to 100 at the same time. The average number is calculated and multiplied by 2/3. The player whose

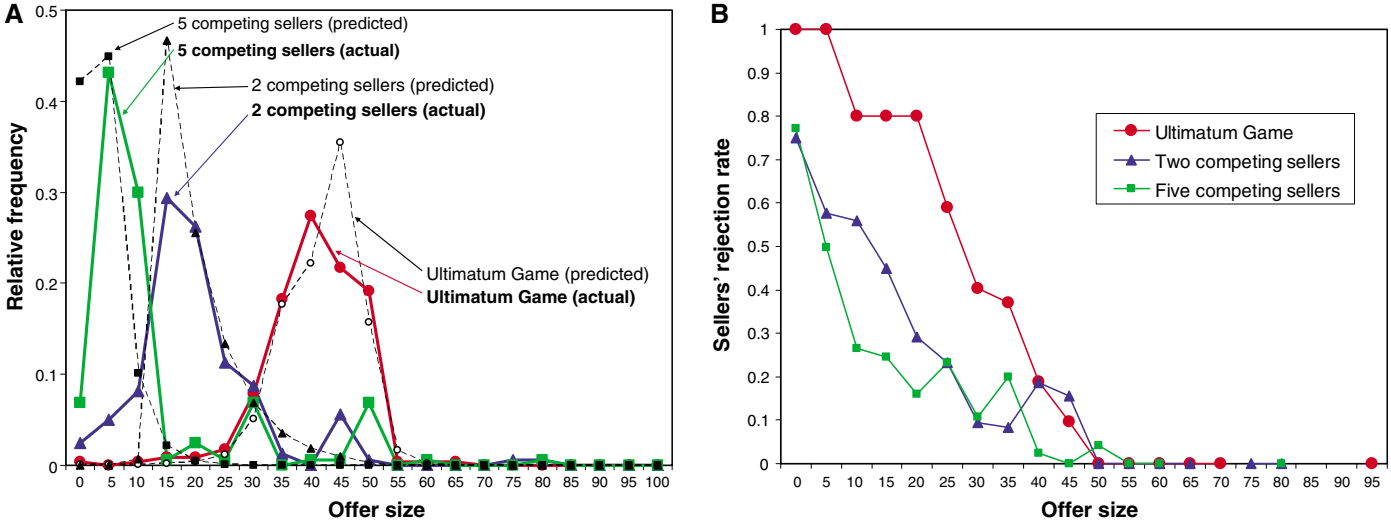

Fig. 2. Behavior of buyers and sellers in the ultimatum game and in market games with competing sellers (*17*). In all games the buyer can make a price offer between 0 and 100 for an indivisible good with value 100. (**A**) The distribution of accepted price offers across conditions. In the ultimatum game most prices are between 40 and 50. If there are two competing sellers, most prices are between 10 and 25; in the case of five competing sellers, the large majority of prices is between 5 and 10. The dotted lines show the predictions of a fairness model for each of the three conditions (*17*). The model has one free parameter to fit the data and combines the theory of inequity aversion (*9*), which assumes heterogeneous preferences for equitable outcomes, with stochastic best reply behavior (*50*). (**B**) Sellers' rejection rate across conditions. More competition leads sellers to reject low offers less frequently.

number is closest to 2/3 of the average (in absolute value) wins a fixed prize. Suppose the numbers are interpreted as the time at which economic actions are taken. Then the game is a simple model of economic situations like introducing a new product in a growing market, or selling stocks in a rising bull market, because players want to move earlier than other players (i.e., choose lower numbers), but the optimal time to move depends on when the average player moves. This game is often called a ''beauty contest,'' after a passage in John Maynard Keynes's influential economics book (*35*). Keynes describes the stock market as a beauty contest in which investors try to figure out what stocks other investors find attractive. Spotting the stocks, which other investors will soon find attractive, earlier enables savvy investors to buy low and sell at a higher price, when the attractiveness of the stocks becomes obvious to all investors and prices rise.

The beauty contest game has been played with dozens of groups of subjects, including small groups of students, highly trained subjects (professional game theorists), and large newspaper contests in which thousands of readers mailed in number entries (*36*–*38*). The basic patterns of numbers are similar across many groups. Figure 3 shows the data from one study (using a multiplier of 0.7 rather than 2/3) with Singapore engineering students (*37*). Number choices are widely distributed. The most common choice was 35, a good choice if you believe choices of others are random (so the expected average will be 50). Some other subjects choose numbers from 20 to 30, as if they anticipate how other subjects are responding to perceived choices that are random.

The equilibrium concept that is most widely used in game theory offers a clear analysis about this game. In a game-theoretic (Nash) equilibrium, every player guesses accurately what others will do and chooses a ''best response'' strategy, which will give the highest expected payoff, given the guesses. The unique equilibrium in the 2/3 game is to choose zero. Intuitively, if players think the average will be a number X, they should choose $(2/3)X$. But if they believe others guess accurately, then other players will choose a best response to $(2/3)X$, which is $(4/9)X$. If all players are reasoning accurately about the reasoning of other players, they should then choose $(2/3)(4/9)X$, and so on. Imposing the restriction that all players guess correctly what other players will do leads to an equilibrium in which choices must equal beliefs, or $X = (2/3)X$, which implies that $X = 0$. Intuitively, if some players choose numbers N above 0, they should anticipate that other players will choose $(2/3)N$ and should lower their choices; the only combination of optimal response and accurate belief is when all players choose 0. Although this reasoning is logically persuasive, it leads to a bad prediction about what will happen, and also gives bad advice. The Nash equilibrium is an inaccurate prediction because strategies are complements: If a player thinks others will pick high numbers, that player should choose a high number too, which means that if limitedly rational players choose numbers that are above the equilibrium of 0, then even rational players should deviate from the equilibrium by choosing high numbers as well.

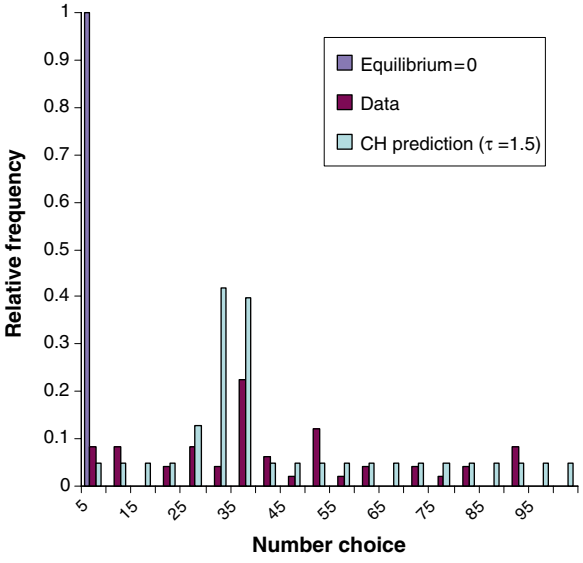

Fig. 3. Number choices and theoretical predictions in beauty contest games. In the beauty contest game players choose numbers from 0 to 100 (*x* axis, bins of five numbers except 0 to 5). The closest number to 0.7 times the average wins a fixed prize. The relative frequency of number choices is shown on the *y* axis (*37*). There are large numbers of choices at 50 and 35. The equilibrium prediction is 0. The CH model (*38*) with $\tau = 1.5$ predicts a spread of choices across the 0 to 100 range, and frequent choices of 35, 29, 26, and 25 (resulting from one to four steps of thinking). The actual mean is 39.9. The CH predicted mean is 34.9.

A business entry game illustrates the opposite pattern, in which limits on rationality have diminished impact when strategies are substitutes. Consider a business entry game involving 12 firms. Firms can stay out of a new market and earn a payoff of 0.5, or can enter a competitive market with a capacity c, where c is the number of firms that can coexist profitably, and c is an even number (2, 4, …10). If c of the firms enter, or fewer, then all firms who enter earn a payoff of 1. If more than c firms enter, then all the entering firms earn 0. A smart firm that is neutral toward risk will enter if it believes the chance that there will be $c - 1$ entrants or fewer is less than 50%. In equilibrium, exactly c firms enter when the capacity is c. If more than c entered, then some firms made a forecasting mistake and should have stayed out; if fewer than c entered, some firms that did not enter should have entered. Notice that near the equilibrium entry choices are strategic substitutes—if firms think too many firms will enter, they prefer to stay out; and if they think too many firms will stay out, they should enter.

In experiments, approximate equilibration occurs across different values of c, even in single-shot game experiments when subjects must choose at the same time without communicating beforehand (*2*). This empirical result is surprising because all firms would prefer to enter and earn 1 than to stay out, so the firms must somehow collectively resolve the problem of coordinating which of the firms will enter (earning the highest payoff) and which will stay out, for different values of c. But approximate equilibration occurs instantly, without negotiation, communication, or learning over time. As Kahneman wrote, ''To a psychologist, it looks like magic'' (*39*).

In the beauty contest game, behavior is reliably far from the equilibrium of 0. In the business entry game, behavior is surprisingly close to the equilibrium of c entries, even without learning or communication. The fact that numbers are strategic complements in the beauty contest game, and entry choices are strategic substitutes in the entry game, provides an important clue to explaining why the beauty contest results are far from equilibrium and the entry game results are close to equilibrium. Can a unified theory of bounded rationality explain the opposite results in the two games, reflecting the different impacts of strategic substitutability and complementarity? The answer is yes.

One class of theories that can explain the conflicting results in both games is a ''cognitive hierarchy'' (CH) approach (*38*, *40*, *41*). In theories of this type, there is a distribution of the number of steps of iterated strategic reasoning that players can do. The fraction of players who do k steps of thinking is $f(k)$. Zero-step players just randomize across their strategies. Higher-step players think they are playing against players who do fewer steps of thinking than they do. The model can be closed mathematically by assuming a distribution $f(k)$, with a precise specification of the beliefs of k-step players about the distribution of players who do less reasoning than they do. A reasonable specification of beliefs is that k-step players believe, overconfidently, that they are responding to players who do 0 to $k - 1$ steps of thinking. A simple specification of $f(k)$ that fits data from

many different games is a Poisson distribution, which is fully characterized by a single parameter τ, the average number of steps of thinking (*38*). When τ is 1.5 (an estimate that fits many games well), the Poisson $f(k)$ drops off very rapidly; only 8% of players do more than three steps of thinking. This low percentage reflects the intuition that because doing many steps of thinking is mentally difficult, and is constrained by working memory, three or more thinking steps are rare without special training or practice. Not surprisingly, experiments across different subject pools also show differences in the average number of thinking steps τ across groups (*38*).

In the beauty contest game with a multiplier of 0.7, the CH model (with $\tau = 1.5$) generates a distribution of numbers across the entire range, a spike of one-step choices at 35, and two-step choices at 29 (Fig. 3). This simple model fits the basic features of the data more accurately than the equilibrium of zero (which was chosen by only 2% of the subjects). The model can sometimes be improved further by including other thinking types, such as players who choose very low numbers because they think, usually mistakenly, that many others will do so as well.

The same CH model that can explain limited progress toward the equilibrium of 0 in the beauty contest game can also predict why players converge close to the equilibrium instantly in the entry game. In the entry game with 12 players, zero-step players ignore the value of c and enter with probability 0.5 for every value of c. One-step players stay out when c is 2, 4, or 6 (because they think there will be too many zero-step entrants) and enter when c is 8 or 10. Two-step players have a more nuanced strategy, responding to their beliefs about the combination of entry by 0-step and 1-step players. When $\tau = 1.5$, two-step players stay out when $c = 2$, because too many 0-step players enter, but they enter when $c = 4$ or 6, because the one-step players stay out for those values of c and make it optimal to enter. They stay out when $c = 8$, because entry by one-step players crowds the market, but they enter when $c = 10$. Including each higher k-step type smoothes out the deviation between the perceived rate of entry of the average of lower-step thinkers, and the equilibrium rate of entry even further, because of strategic substitution (players stay out when they think too many players will enter, and enter when they think too few will enter). The result is an aggregate entry function, averaging across players using different numbers of steps of thinking, which predicts entry that rises monotonically in the capacity c, but also predicts too much entry at low c and too little entry at high c (Fig. 4). This simple model is one explanation for the "magic" of approximate equilibrium entry rates without learning or communication in experiments.

The beauty contest and entry games show how the same unified model of bounded rationality, made precise in the cognitive hierarchy approach, can explain when behavior is far from equilibrium, in the beauty contest game, and when behavior is surprisingly close to equilibrium, in the entry game. In the beauty contest game, strategies are complements, so players who do limited thinking cause even rational players to choose high numbers. In the entry game, choices are substitutes so the influence of boundedly rational players on aggregate behavior is largely erased.

Strategic substitutability and complementarity can also play an important role in financial markets, where these forces can amplify or diminish the impact of limits to rationality on aggregate outcomes. This can be illustrated by prediction markets for bets on events, and stock markets. In prediction markets, an upcoming event is defined precisely so that bets can be settled, such as the future price at which commodities will sell in a few months, the outcome of a political election, or a newsworthy happening like the capture of Osama Bin Laden. In prediction markets for events, assets are created that pay a fixed sum if the event occurs. Traders buy and sell the asset. The price that is established, normalized by the payout, gives a market-wide probabilistic estimate that the event will occur. For example, the Tradesports Web site (www.tradesports.com) prices on 13 October 2005 implied a 19% probability that Osama Bin Laden would be captured by June 2006.

Many studies have found that prices in prediction markets are remarkably accurate forecasts of events (*42*). Orange juice prices are very sensitive to cold weather in Florida, which causes freezes and drives up prices by reducing supply. Futures prices for juice are therefore influenced by forecasts of freezes. However, one study showed that futures prices for juice are more accurate forecasts of the chance of a freeze than U.S. National Weather Service meteorological forecasts (*43*). The Iowa Political Stock Markets (www.biz.uiowa.edu/iem) also forecast actual election results more accurately than expensive opinion polls in more than 75% of hundreds of different elections at many levels and in different countries (*44*). Sixty days before presidential elections, the Iowa market absolute forecast error of vote share is only 2% (*28*, *45*).

Prediction markets forecast accurately because poorly informed traders provide a clear opportunity for better-informed traders to make money. Better-informed traders who express their confidence by making large trades can be sure to collect when an event either does or does not occur, at a known time in the near future. For example, if a better-informed trader knows that the asset is undervalued (i.e., the event is more likely to occur relative to the prevailing market opinion), he will buy the asset from the poorly informed traders. Thus, substitutability again diminishes the impact of less rational actors.

A contrasting case is stock markets. Stock prices respond to new information rapidly, and using public information (like past price trends) to beat the market is difficult. At the same time, because stocks are claims on profits of an ongoing enterprise, there is never a fixed future time at which the true value of a firm is established and bets are settled once and for all. As a result, well-informed traders cannot always guarantee a profit at the expense of traders with limited rationality. In fact, institutional constraints such as performance pressure, and impediments to selling shares short (betting that stock prices will fall), mean that if stock prices are bad estimates of the value of a firm, large well-capitalized investors cannot always guarantee a profit by betting against the market (*46*). The fact that "noise traders" add volatility to stock prices creates a special kind of risk for smart investors, which makes them reluctant to bet against noise traders and bring stock prices closer to the fundamental value of firms (*47*). As a result, when there are institutional constraints trading strategies can be strategic complements, so that well-informed investors can be forced to follow a poorly informed crowd, rather than betting against it. A striking example is the mispricing of "twin shares," such as Royal Dutch/Shell. Royal Dutch/Shell is a single company whose economic value, until very recently, was divided into two separate shares, Royal Dutch

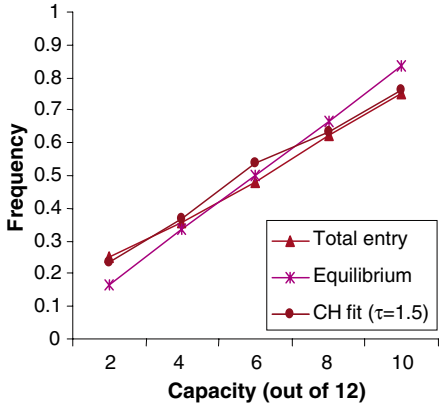

Fig. 4. Rates of entry in business entry games and theoretical predictions (in percentage terms). Actual and predicted rates of entry in games with $N = 12$ firms and capacity c equal to 2, 4, 6, 8, and 10. Identity line (*) shows Nash equilibrium entry rates (entry equals capacity). Actual entry in experiments [▲, (*38*)]. Entry predicted by CH model (•). Actual entry is monotonic in capacity c, but there is too much entry for low c and too little entry for high c. Actual entry rates (▲) are close to the Nash equilibrium (*). The entry rates predicted by CH (•) are consistent with the deviations between actual and equilibrium entry rates.

shares (traded in Amsterdam) and Shell shares (traded in New York). Based on a merger agreement, the Royal Dutch shareholders are legally entitled to 60% of the combined entity's cash flows and the Shell company is entitled to 40%. If the prices of the shares reflect their economic value, then the ratio of Royal Dutch and Shell share prices should always be 60/40, or 1.5. In fact, the ratio of the two stock prices has wandered away from 1.5 for many years, from 30% too low in 1981 to 15% too high in 1996 (*48*). If the ratio is too high, investors can potentially profit by selling Royal Dutch shares short and buying Shell shares and waiting for the ratio to fall toward 1.5. But betting that the price ratio will revert to its economic value of 1.5 is inherently risky because markets are volatile. When the ratio is well above 1.5, it often rises even further away. In fact, hedge funds that made highly leveraged bets that the ratio would return to 1.5 are exposed to risk. If investors with short horizons are nervous about betting heavily on reversion to the 1.5 ratio, their nervousness keeps them from making large bets on rapid reversion, which in turn keeps that ratio from rapidly reverting to 1.5, which validates their nervousness.

The contrast between prediction and stock markets reiterates the basic theme of this review. In prediction markets there is a known future time at which bets will be settled based on event. As a result, trades are strategic substitutes because a well-informed trader can profitably bet against a poorly informed one with little risk. But stock values are never decided at a clear point in the future. So prices can drift far from economic fundamentals for many years, as the Royal Dutch/Shell case shows. Rational traders who recognize the mispricing and bet against it might have to wait years to earn their due. As Keynes wrote, "markets can stay irrational longer than you can stay liquid." So, trading strategies are complementary when rational traders have an economic incentive to go along with the crowd for extended periods of time.

Alternative Models and Future Directions

The examples discussed in this review show that heterogeneity in other-regarding preferences and bounded rationality, along with the structure of social interactions, determine when collective outcomes are close to predictions based on rationality and self-regarding preferences, or are far from those predictions. Under certain conditions, models based on self-regarding preferences and homogeneous rationality predict aggregate behavior rather well, even though many people exhibit rationality limits and other-regarding preferences (*49*). However, under strategic complementarity, even a small proportion of other-regarding or boundedly rational players may suffice to generate collective outcomes that deviate sharply from models of Economic Man. The new models of heterogeneous social preferences and bounded rationality explain these puzzling results in a unifying way because they explicitly take heterogeneity and incentive interactions between different types of individuals into account. Therefore, they can explain when Economic Man dominates aggregate outcomes and when he fails to do so.

There are many other social domains in which the mixture of heterogeneous social preferences and rationality limits are likely to create profound effects on aggregate behavior. In companies, matching different workers to appropriate jobs, based on their preferences and rationality, implies interesting variation in the nature of employment contracts and firm-level outcomes. Designing well-functioning economic institutions, to help poor countries grow richer, depends on a good model of human behavior. Governments, philosophers, and lawyers are concerned about crafting policies that protect consumers with rationality limits that are swamped by information and choices, while protecting the freedom of choice of expert consumers. Understanding the biological basis for differences in preferences and rationality bounds, and locating their neural circuitry, will also help social sciences, and will inform neuroscience about important kinds of higher-order cognition. A better understanding of when the useful caricature of Economic Man dominates markets, or is dominated by social preferences and rationality limits, will inform all these enterprises and could lead to a more unified, and powerful, approach to both biological and social sciences of human behavior.

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Two-Way Laser Link over Interplanetary Distance

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The detection and precise timing of low-energy laser pulses transmitted over interplanetary distances will enable advances in fundamental physics and solar system dynamics (*1*), as well as high-bandwidth deep-space communications (*2*, *3*). The MESSENGER (MErcury Surface, Space ENvironment, GEochemistry, and Ranging) spacecraft (*4*), launched 3 August 2004, is carrying the Mercury Laser Altimeter (MLA) (*5*) as part of its instrument suite on its 6.6-year voyage to Mercury. In an experiment performed before an Earth flyby, the MLA successfully ranged to Earth and received laser pulses from the NASA Goddard Geophysical and Astronomical Observatory (GGAO) (*6*).

The only other deep-space laser ranging demonstration occurred before MLA in 1992, when two ground-based lasers were pointed toward the Galileo spacecraft and the signals were detected at a distance of 6×10^6 km as streaks of light by the spacecraft's camera (*7*). In contrast, the MLA Earth-ranging experiment operated like an asynchronous transponder (*8*), in which space-based and Earth-based laser terminals independently fired timed pulses at each other, with the transmitted and received pulse times linked by means of a stable spacecraft clock. The times of the paired observations were used to solve for a common range and clock offset (*6*).

The MESSENGER spacecraft clock is an ovenized quartz oscillator (*4*) that measures mission elapsed time (MET) and is periodically synchronized to coordinated universal time (UTC) by the terrestrial reference system terrestrial dynamic time. Over the test period 26 to 31 May 2005, the spacecraft clock, to which the MLA is periodically calibrated, was stable to approximately one part per billion (ppb).

In three observing opportunities, the MLA laser was fired for 5-hour periods while the spacecraft scanned Earth at a rate of 16 μrad s^{-1} along lines spaced 32 μrad apart, for a total scan area of 3.2 by 3.2 mrad. Event timers logged pulse transmission and arrival times at GGAO, referenced to UTC within 100 ns absolute time. A digital oscilloscope at a frequency of 1 GHz also recorded the received pulse shapes. Sixteen consecutive pulses were recorded at 19:47:24 UTC on 27 and 24 May; more were recorded at 19:42:02 UTC on 31 May.

Simultaneously, a laser at GGAO was beamed upward toward MLA. The uplink pulses, along with noise triggers from the sunlit Earth, were received within a 15-ms range window during each 125-ms shot interval. Inspection of the stored instrument data revealed 90 pulses over a 30-min time frame, 17 on multiple channels, whose timing matched the GGAO fire times.

The interpretation of these events as downlink and uplink ranges required a joint solution (*6*) for spacecraft clock and state parameters (Fig. 1). The solution yielded a clock offset and drift rate at the origin time and the range as a function of time at the spacecraft (Table 1) (*9*). Downlink observations were fit with a root mean square residual of 0.39 ns, whereas uplink observations suffered from marginal signal link and were fit with an rms residual of 2.9 ns. Formal standard deviations indicate that the range was determined with an accuracy of ±20 cm. Our range agrees with that derived from the reconstructed ephemeris from X-band Doppler tracking (7.2 GHz uplink; 8.4 GHz downlink) to within 52 m. This experiment has demonstrated subnanosecond laser pulse timing and accomplished a two-way laser link at interplanetary distance. In addition, it established a distance record for laser transmission and detection.

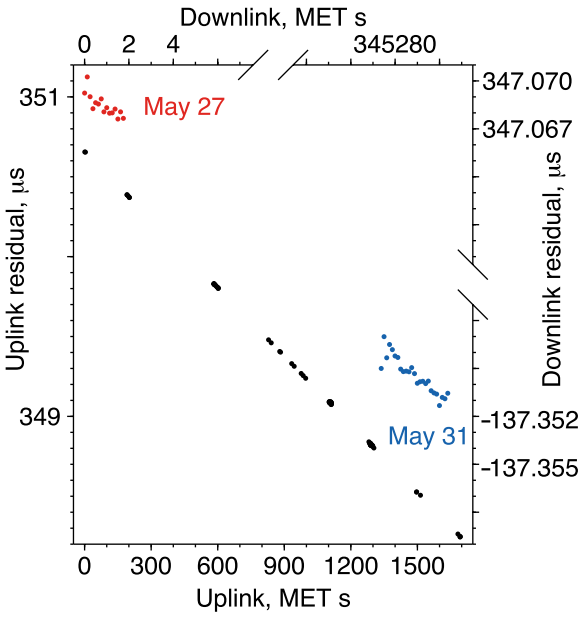

Fig. 1. Pulse-received times at MLA and GGAO. The graph shows that ground laser pulses (black symbols) were received by MLA ~0.35 ms earlier than predicted. Similarly, the ground-receive time of MLA pulses was ~0.34 ms earlier on 27 May (red symbols) but ~0.14 ms later on 31 May (blue symbols).

Table 1. Solution parameters.

Parameter	Laser link solution	Spacecraft ephemeris	Difference
Range (m)	23,964,675,433.9 ± 0.2	23,964,675,381.3	52.6
Range rate (m s^{-1})	4,154.663 ± 0.144	4,154.601	0.062
Acceleration (mm s^{-2})	−0.0102 ± 0.0004	−0.0087	−0.0015
Time (s)	71,163.729670967 ± 6.6×10^{-10}	71,163.730019659	0.000348692
Clock drift rate (ppb)	1.00000001559 ± 4.8×10^{-10}	1.00000001564	-3.2×10^{-10}

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Supporting Online Material

www.sciencemag.org/cgi/content/full/311/5757/53/DC1
Materials and Methods
Table S1
References and Notes

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The Distance to the Perseus Spiral Arm in the Milky Way

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We have measured the distance to the massive star–forming region W3OH in the Perseus spiral arm of the Milky Way to be 1.95 ± 0.04 kiloparsecs (5.86 × 10^{16} km). This distance was determined by triangulation, with Earth's orbit as one segment of a triangle, using the Very Long Baseline Array. This resolves the long-standing problem that there is a discrepancy of a factor of 2 between different techniques used to determine distances. The reason for the discrepancy is that this portion of the Perseus arm has anomalous motions. The orientation of the anomalous motion agrees with spiral density-wave theory, but the magnitude of the motion is somewhat larger than most models predict.

Massive stars and their associated bright regions of ionized hydrogen trace the spiral arms of galaxies. However, for our galaxy, the Milky Way, our view from the interior makes it difficult to determine its spiral structure. In principle, one can construct a simple model of the rotation speed of stars and gas as a function of distance from the center of the Milky Way. Then, if one measures the line-of-sight component of the velocity of a star or interstellar gas, one can determine its distance by matching the observation with the model prediction (that is, a kinematic distance). Knowing the distances to star-forming regions, one can then locate them in three dimensions and construct a "plan view"—a view from above the plane—of the Milky Way. Unfortunately, many problems arise when constructing a plan view of the Milky Way, including (i) difficulties in determining an accurate rotation model (which requires values for the distance and orbital speed of the Sun from the center of the Milky Way), (ii) distance ambiguities in some portions of the Milky Way (where an observed velocity can occur at two distances), and (iii) departures from circular rotation (as might be expected for spiral structure). Progress has been made on the first two problems. For example, many kinematic distance ambiguities can be resolved by interferometric studies of hydrogen absorption at radio frequencies, because distant sources will show a greater velocity range for hydrogen absorption than will near sources (*1*). However, the third problem, noncircular motions, is fundamentally much harder to address.

The Perseus arm is the nearest spiral arm outward from the Sun (Fig. 1) (*2*, *3*). There are many star-forming regions in the Perseus arm for which distances have been estimated from the difference between the observed and intrinsic luminosities of massive young (O-type) stars. Toward Galactic longitudes from 132° to 138°, such luminosity distance estimates are ≈2.2 kiloparsecs (kpc) (*4*). However, kinematic distance estimates for these regions are much greater. Stars and gas in this region of the Perseus arm are observed to move with line-of-sight velocities of about −45 km s^{-1}, relative to the local standard of rest (LSR) (*5*). Assuming that the Milky Way rotates at 220 km s^{-1}, independent of the distance from its center, and that the Sun is at a distance of 8.5 kpc from the center (*6*), the observed Perseus arm velocities occur at distances of >4 kpc. The discrepancy between distances based on stellar luminosities and velocities has never been resolved.

The problem of determining the distance to the Perseus arm can be resolved by determining an accurate distance to a massive star–forming region in the arm. The best and most reliable method for measuring distance in astronomy is called a trigonometric parallax. A trigonometric parallax is determined by observing the change in position of a star, relative to very distant objects such as quasars, as Earth moves in its orbit about the Sun. The parallax is simply the maximum angular deviation of the apparent position from its average position over a year. The deviation in position of a source over a year is very small. For example, the parallax for a source at a distance of 2 kpc, or about one-quarter of the distance to the center of the Milky Way, is only 0.5 milli–arc second (mas).

The distance D to a source is easily calculated from its parallax π by triangulation: D(kpc) = 1/π(mas). Thus, one needs a measurement accuracy of 0.05 mas to achieve 10% accuracy for a source at 2 kpc distance, which would be sufficient to resolve the Perseus arm discrepancy. By comparison, trigonometric parallaxes obtained by the Hipparcos satellite (*7*) typically have uncertainties of only ≈1 mas, which is inadequate for our purposes.

An ideal candidate for a trigonometric parallax measurement is the massive star–forming region W3OH, located at Galactic longitude 134° and near O-type star associations. W3OH has strong methanol masers (*8*, *9*), which can serve as bright, relatively stable beacons for astrometric observations at radio wavelengths. In this paper, we describe observations with the Very Long Baseline Array (VLBA), consisting of 10 radio telescopes spanning Earth from Hawaii to New England to the Virgin Islands and operated by the National Radio Astronomy Observatory (*10*), which allowed us to achieve an extraordinarily accurate (0.01-mas) paral-

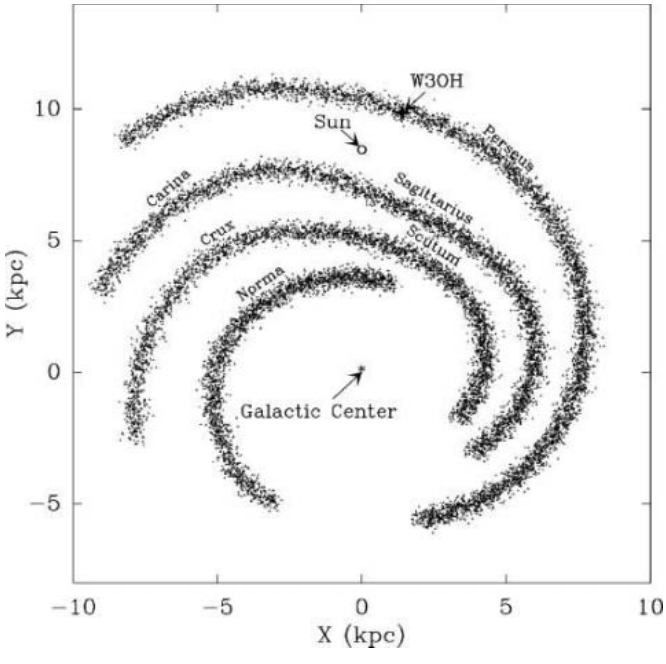

Fig. 1. Plan view of the Milky Way as seen from its north pole. Estimated locations of spiral arms (*2*, *3*) are indicated by the large number of dots and labeled by a prominent constellation onto which they are projected. The locations of the Galactic Center, Sun, and W3OH are indicated.

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lax for W3OH and to resolve the long-standing problem of determining the distance to the Perseus arm. Our results also provide valuable information that can be used to test spiral density-wave models of the Milky Way.

We observed W3OH and three compact extra-Galactic radio sources for 8 hours on each of five epochs in order to measure the position of W3OH (using its methanol masers as astrometric targets) relative to extra-Galactic radio sources. The dates of observation were 30 July and 21 October 2003, and 30 January, 23 April, and 25 July 2004. These dates sample well the peaks and nulls of the sinusoidal trigonometric parallax signature, caused by observing the source at different positions in Earth's orbit about the Sun. This sampling ensures that we can separate the linear proper motion (caused by projections of Galactic rotation, as well as the peculiar motion of W3OH and the Sun) from the sinusoidal parallax effect.

We switched rapidly among W3OH and the background sources, repeating the following pattern: W3OH, J0235+622, W3OH, J0231+628, W3OH, J0230+621. Sources were changed every 40 s, typically achieving 30 s of on-source data each time. We used a methanol maser as the phase-reference source, because it is considerably stronger than the background sources and could be detected on individual interferometer baselines with signal-to-noise ratios exceeding 100 in the available on-source time.

We discuss details of the calibration procedures in the supporting online material. After calibration, we made an image of a strong reference maser channel. We show the first and last epoch images of the reference spectral channel at an LSR velocity, v_{LSR}, of -44.2 km s^{-1} in Fig. 2. One can see that there is little change in the masers over a year. In fig. S1, we show an image at one epoch of each of the background radio sources. All three background sources are compact (<0.5 mas) and dominated by a single component.

In order to provide the data needed to measure the parallax and proper motion (on the plane of the sky), we fitted two-dimensional Gaussian brightness distributions to the nine brightest maser spots and the three background radio sources for all five epochs. In Fig. 3, we show plots of the positions of one maser spot in W3OH relative to the three background radio sources. The change in position of a maser spot relative to a background radio source was then modeled by the parallax sinusoid in each coordinate, completely determined by one parameter (the parallax), and by a linear proper motion in each coordinate. Tables 1 and 2 list the parameters of the fits.

An unweighted average parallax for the nine maser spots of W3OH measured against each of the background sources yields parallax estimates of 0.502 ± 0.011 mas using J0230+621, 0.526 ± 0.014 mas using J0231+628, and 0.515 ± 0.015 mas using J0235+622. These results are consistent within their formal errors, and a weighted average of these three parallaxes yields 0.512 ± 0.007 mas.

The parallaxes from the three calibrators increase slightly with increasing maser-calibrator separation, suggesting that atmospheric systematics may not have been entirely removed. However, with only three calibrators, it is difficult to assess the significance of this effect. In order to allow for the possibility of some uncompensated atmospheric systematics, we estimate a systematic component of the parallax uncertainty of 0.007 mas. Thus, our final parallax estimate is 0.512 ± 0.007 (statistical) ±0.007 (systematic) mas. The statistical and systematic uncertainties are independent, and combining them quadratically yields a parallax of 0.512 ± 0.010 and, hence, a distance of 1.95 ± 0.04 kpc.

Our trigonometric parallax estimate is consistent with a similar measurement of 2.04 ± 0.07 kpc using H_2O masers associated with the Turner-Welch (TW) object, a protostellar object projected 5 arc sec from W3OH (*11*). These distances for W3OH in the Perseus spiral arm conclusively resolve the long-standing discrepancy between its kinematic distance of 4.3 kpc and a luminosity distance of ≈2.2 kpc, based on O-type stars nearby in the same spiral arm (*4*). The luminosity distance is consistent with the trigonometric parallaxes, and W3OH must have a large kinematic anomaly.

Table 2 presents the proper motion results. The individual proper motions span a range of about 0.3 and 0.2 mas year^{-1} (or 3 and 2 km s^{-1}) in the eastward and northward directions. This is comparable to the spread in hydroxyl (OH) maser proper motions from the same region of W3OH (*12*). Thus, the dispersion in the proper motions is likely to come

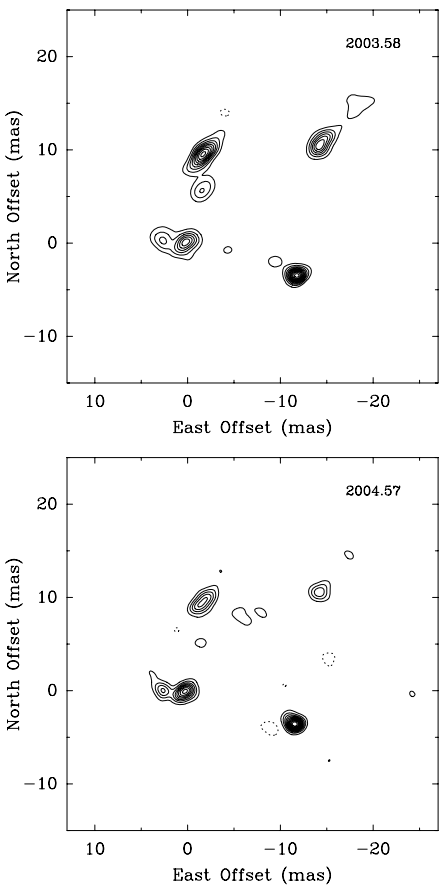

Fig. 2. The first and last epoch maps (at dates indicated in the upper right corner) of 12-GHz methanol masers toward W3OH. This map contains emission from one spectral channel at $v_{LSR} = -44.2$ km s^{-1}; the maser reference spot is at (0,0). The maser emission structures change little over the time range of our parallax measurements. Only the two brightest and most compact spots near (0,0) and (–12,–3) mas were used for the parallax measurement. The contour levels are integer multiples of 2 Jy per beam, with negative values dashed and the zero contour suppressed. The restoring beam size is 1.2 mas. The origin of the maps is α(J2000) = 02 27 03.8192 and δ(J2000) = 61 52 25.230.

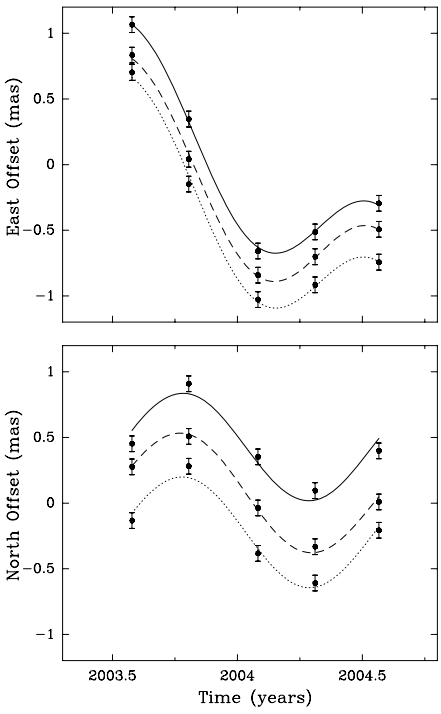

Fig. 3. Position versus time for the reference maser spot [the strong maser spot near (0,0) in Fig. 2] at $v_{LSR} = -44.2$ km s^{-1} relative to three background radio sources. The top and bottom panels show the eastward and northward offsets, respectively. The large difference in position between W3OH and each background source has been removed, and the data for the different background sources have been offset for clarity. In each panel, the top, middle, and bottom data are for the background sources J0230+621, J0231+628, and J0235+622, respectively. Also plotted are the best-fitting models, specified by five parameters: one for the parallax and two for the proper motion in each coordinate.

Table 1. Columns one through four give the maser spot number, the east and north position offsets [relative to α(J2000) = 02 27 03.8192 and δ(J2000) = 61 52 25.230], and the LSR velocity, respectively. Columns five through seven give the parallax estimates for W3OH relative to the three extra-Galactic sources J0230+621, J0231+628, and J0235+622. Spot 4 is the reference maser; emission from spots 3 through 5 can be seen in Fig. 2, which displays emission in a single spectral channel centered at -44.2 km s^{-1}. Positions and parallaxes for other maser spots were determined from images in other spectral channels.

Spot	Offset east (mas)	Offset north (mas)	v_{LSR} (km/s)	W3OH/J0230+621 parallax (mas)	W3OH/J0231+628 parallax (mas)	W3OH/J0235+622 parallax (mas)
1	−16.502	−1.317	−43.5	0.535 ± 0.048	0.559 ± 0.050	0.549 ± 0.055
2	−0.145	0.163	−43.8	0.513 ± 0.021	0.535 ± 0.032	0.524 ± 0.042
3	−11.760	−3.456	−44.2	0.469 ± 0.023	0.495 ± 0.040	0.483 ± 0.039
4	0.179	0.113	−44.2	0.439 ± 0.018	0.463 ± 0.037	0.452 ± 0.036
5	−7.683	8.925	−44.6	0.556 ± 0.044	0.581 ± 0.052	0.568 ± 0.045
6	70.958	60.077	−45.8	0.493 ± 0.020	0.515 ± 0.036	0.505 ± 0.040
7	69.766	−59.651	−42.3	0.495 ± 0.040	0.518 ± 0.052	0.508 ± 0.041
8	69.500	−59.703	−42.7	0.488 ± 0.024	0.513 ± 0.041	0.503 ± 0.045
9	20.957	−126.030	−43.1	0.529 ± 0.032	0.552 ± 0.055	0.543 ± 0.054

Table 2. Column one gives the maser spot number. Columns two and three give the motion on the plane of the sky in the eastward and northward directions, μ_x and μ_y, respectively, of a maser relative to the extra-Galactic source J0230+621. Columns four and five and six and seven give motions relative to extra-Galactic sources J0231+628 and J0235+622. Typical uncertainties for individual proper motions are ±0.09 mas year^{-1}. The unweighted mean proper motion for W3OH is −1.204 ± 0.02 mas year^{-1} (−11.1 ± 0.2 km s^{-1}) eastward and −0.147 ± 0.01 mas year^{-1} (−1.3 ± 0.1 km s^{-1}) northward.

Spot	W3OH/J0230+621		W3OH/J0231+628		W3OH/J0235+622	
	μ_x (mas year^{-1})	μ_y	μ_x (mas year^{-1})	μ_y	μ_x (mas year^{-1})	μ_y
1	−1.020	−0.134	−1.125	−0.003	−1.097	+0.044
2	−1.315	−0.217	−1.419	−0.085	−1.392	−0.037
3	−1.068	−0.272	−1.172	−0.141	−1.145	−0.093
4	−1.153	−0.340	−1.257	−0.209	−1.230	−0.161
5	−1.013	−0.226	−1.117	−0.095	−1.090	−0.047
6	−1.112	−0.339	−1.216	−0.208	−1.189	−0.160
7	−1.175	−0.257	−1.279	−0.125	−1.252	−0.078
8	−1.071	−0.205	−1.176	−0.074	−1.148	−0.026
9	−1.363	−0.260	−1.467	−0.129	−1.440	−0.081

both from small internal motions of the maser spots of a few kilometers per second and from a measurement error of ±0.1 mas year^{-1}(±1 km s^{-1}). Because of the limited number of methanol masers mapped and the small velocity spread expected for methanol masers (based on the close correspondence with OH masers), we make no attempt to fit an expanding model to the data.

The mean proper motion in the eastward and northward directions, obtained from an unweighted average of all the data, is -1.204 ± 0.02 and -0.147 ± 0.01 mas year^{-1}, respectively, where the uncertainties are standard errors of the mean. Thus, the uncertainty in the mean proper motion translates to an impressive 0.2 km s^{-1} at a distance of 1.95 kpc. Allowing for a spread of ±3 km s^{-1} for the internal motions of the masers, we adopt a 1σ uncertainty of 1 km s^{-1} in each component of the average of our motions.

In order to study the three-dimensional motion of W3OH in the Galaxy, we converted its radial and proper motion from the equatorial heliocentric reference frame, in which they are measured, into a Galactic reference frame. A convenient Galactic frame is one moving with a circular velocity about the center of the Galaxy at the position of W3OH; that is, an LSR for W3OH. We followed published methods (*13*), adopting the International Astronomical Union standard values for the distance from the Sun to the Galactic Center of 8.5 kpc and for the rotation speed of the LSR about the Galactic Center of 220 km s^{-1}. When removing the peculiar motion of the Sun relative to the LSR, we adopted solar motion values determined by Hipparcos (*14*).

The Galactocentric distance of W3OH is 9.95 kpc, and its rotation velocity about the Galactic Center is 206 ± 10 km s^{-1}. This velocity uncertainty is far above our measurement error and is dominated by an uncertainty of about ±10 km s^{-1} for the rotation speed of the Galaxy. However, the difference in the rotation velocities of the Sun and W3OH is largely insensitive to the value adopted for the Galaxy's rotation speed. Assuming a constant rotation speed in the Galaxy between 8.5 and 9.95 kpc from its center (the Galactocentric radii of the Sun and W3OH, respectively), the difference between the rotation speed of W3OH and the Galaxy is 14 ± 1 km s^{-1} in the sense that W3OH is orbiting slower than the Galaxy spins. The motion of W3OH toward the Galactic Center is 17 ± 1 km s^{-1}. The motion of W3OH toward the north Galactic pole is -0.8 ± 0.5 km s^{-1}. Combining the three components, the total peculiar motion of W3OH is 22 km s^{-1}. Essentially all of the peculiar motion is in the plane of the Galaxy, as expected for a massive star–forming region.

For an axially symmetric distribution of mass in the Galaxy, rotational velocities cannot fall more rapidly with Galactocentric radius r than $1/\sqrt{r}$. The 14 km s^{-1} slower rotation of W3OH, compared to its LSR, would therefore require essentially no mass between the Galactocentric radius of the Sun (8.5 kpc) and W3OH (9.95 kpc). This seems unlikely and provides motivation for a nonaxisymmetric mass distribution, such as that provided by spiral density-wave theory.

Spiral density waves might be able to account for some of the peculiar motion of W3OH. In order to maintain a spiral density wave, material flowing into a trailing arm would be expected to acquire motion components inward and counter to Galactic rotation (*15*), as we have observed. However, for density contrasts between arm and interarm regions of ≈10%, peculiar velocity components of only ≈5 km s^{-1} are expected. This is smaller than we observe for W3OH. However, calculations suggest that a spiral shock embedded in a background density wave might lead to velocity jumps in molecular material of the magnitude that we observe for W3OH (*16*).

Gravitational forces from nearby forming stars, such as the TW object, and from massive molecular clouds should contribute ≈5 km s^{-1} to the motion of W3OH. Indeed, the TW object has been observed to move at ≈10 km s^{-1} with respect to W3OH (*11*). Depending on the relative masses of these and other stars and gas in the region, some of the 22 km s^{-1} peculiar motion of W3OH might be explained by local

gravitational effects. Additionally, the giant molecular cloud material that existed before the formation of the stars in the W3OH region could have been accelerated by shocks associated with supernovae in the region (*17*–*19*). Overall, it remains to be seen whether one can account for the peculiar motion of W3OH in the context of the spiral density-wave paradigm.

We have established that the VLBA can achieve a parallax accuracy of 0.01 mas and a proper motion accuracy of better than 1 km s^{-1} for Galactic sources with only five observations spanning 1 year. With this accuracy, the VLBA can be used to measure distances to 10 kpc with better than 10% accuracy, which is approximately a factor of 100 better than the Hipparcos satellite. Based on these results, we believe that the VLBA, and ultimately the Japanese Very Long Baseline Interferometric project VERA [VLBI Exploration of Radio Astrometry (*20*)], can map the spiral structure and full kinematics of massive star–forming regions in the Milky Way.

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Quantum Dynamics of a d-Wave Josephson Junction

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Here we present the direct observation of macroscopic quantum properties in an all high-critical-temperature superconductor d-wave Josephson junction. Although dissipation caused by low-energy excitations is expected to strongly suppress macroscopic quantum effects, we demonstrate energy level quantization in our d-wave Josephson junction. The result indicates that the role of dissipation mechanisms in high-temperature superconductors has to be revised, and it may also have consequences for the class of solid-state "quiet" quantum bits with superior coherence time.

In terms of engineering quantum-information applications and searching for physical systems where quantum mechanics can be applied at a macroscopic level, superconductors have inherent advantages (*1*). Indeed, the detection of macroscopic quantum tunneling and energy-level quantization effects in conventional Josephson junction (JJ) circuits (*2*) has enabled the fabrication of superconductive quantum devices based on low–critical-temperature superconductor (LTS) Josephson junctions. The quantum superposition of distinct macroscopic states (*3*, *4*) and the observation of Rabi oscillations (*5*–*9*) have also been reported in these devices. Superconductive quantum devices take advantage of a well-developed gap in the excitation spectrum of quasiparticles, which favors less dissipation, and the coherence of the superconducting state helps to achieve sufficiently long phase-coherence times. First-principle design and operation of superconducting devices has been demonstrated, and simple quantum protocols now appear feasible (*1*, *10*). High–critical-temperature superconductors (HTSs) are another candidate for quantum circuitry because of a d-wave order-parameter symmetry (*11*), a property which favors a naturally bistable system (a qubit) working in a particular "quiet" configuration (*12*–*15*). The operating point of the qubit is protected from external field fluctuations already at the classical level (*15*). The interest in HTS quantum systems is not only limited to quantum circuitry design, but also addresses fundamental issues on the nature of superconductivity and dissipation and the coherence in such objects.

However, one of the main arguments against HTS qubits based on systems with d-wave order-parameter symmetry is the presence of low-energy excitations inducing dissipation (*11*, *16*–*18*), a property which is expected to prevent the occurrence of macroscopic quantum phenomena, which are the key element for qubits. Here we report the observation of energy-level quantization in d-wave JJ, a clear signature of macroscopic quantum behavior and an indication that the dissipation in a d-wave JJ is low enough to allow the formation of the "sharp" energy levels required for a qubit. The result also indicates that the role of dissipation mechanisms in HTSs has to be revised and that d-wave devices do possess a macroscopic quantum degree of freedom.

The dynamics of a current-biased JJ is well established for LTSs. Within the resistively and capacitively shunted junction (RCSJ) model (Fig. 1A) (*19*), the Josephson inductance L_J and capacitance C_J act as an anharmonic LC resonator (at zero voltage) with resonance frequency $\omega_P = (L_J C_J)^{-1/2}$. The Josephson inductance is given by $L_J = \varphi_0/2\pi I_c \cos\varphi$, where I_c is the critical current, φ is the phase difference across the junction, and $\varphi_0 = h/2e$ is the superconducting flux quantum, where h is Planck's constant and e is the charge of an electron. For bias currents I close to the critical current I_c, the junction potential $U(\varphi)$ can be approximated by a cubic potential (Fig. 1B). The phase may escape from the well either by thermal activation or by tunneling through the barrier potential, and it corresponds to the junction switching from the zero voltage state to a finite voltage state. The escape is dominated by tunneling (*20*) at low temperature. The quantum bound states formed in the well with energy E_n, where n indicates the nth energy level, are shown in Fig. 1B. Only the

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ground state is populated at temperatures smaller than the energy-level separation. The quantum states can be observed spectroscopically by inducing a resonant transition between the ground state and excited states by applying microwaves at frequencies $\nu_{0n} = (E_n - E_0)/h$. The width of the first excited energy level is determined by the energy decay rate into the ground state, and is given by $1/\tau = \mathrm{Re}(Y)/C_J = \nu_{01}/Q$, where τ is the lifetime of the first excited level, $\mathrm{Re}(Y)$ is the real part of the frequency-dependent total shunting admittance Y causing dissipation, and Q is the quality factor of the junction (*21*).

We fabricated highly hysteretic (*22*), tunnel-like $YBa_2Cu_3O_{7-\delta}$ (YBCO) grain boundary JJs using the bi-epitaxial technique (*23*, *24*). Junctions were formed at the interface between a (103) YBCO film grown on a (110) $SrTiO_3$ (STO) substrate and a c-axis film deposited on a (110) CeO_2 seed layer. The orientation of the order parameter in the two electrodes is shown in Fig. 2A. In this experiment, we focused on JJs where a lobe of the order parameter of one electrode is facing a node in the other electrode. This configuration yields a natural double-degenerate ground state of interest for future qubit applications (*15*). The intrinsic sources of dissipation due to nodal quasiparticles and surface Andreev bound states are maximally enhanced.

The stray capacitance C_S of the electrodes, caused by the large dielectric constant of the STO substrate at low temperature (*25*) (dielectric constant $\varepsilon_r > 10{,}000$), and the kinetic inductance L_k, caused by c-axis transport in one of the electrodes, can be taken into account by a modified RCSJ model (Fig. 2, B and C). The energy-level separation in this simple model is given by $h\nu_{01} = (h/2\pi)[(L_J + L_k)C_S]^{-1/2}$ (*26*).

The enhancement of the escape rate is measured under microwave irradiation to detect the energy levels. This allows us to analyze the bias current dependence of the energy-level separation and determine the width of the first excited level, which gives information on the dissipation processes in the junction. By repeatedly ramping the bias current I from zero at a constant rate, we determined the switching current probability distribution $P(I)$ from the zero voltage state to the finite voltage state. This switching probability can be directly related to the escape rate $\Gamma(I)$ (*27*).

Microwaves at fixed frequency ν_{mw} were transmitted to the junction via a dipole antenna at a temperature below the cross over value, T_{cr}, separating the thermal and quantum regimes (*22*). When ν_{mw} of the incident radiation (or multiples of it) coincides with the bias current–dependent level separation of the junction, $\nu_{01}(I) = m\nu_{mw}$, the first excited state is populated (*28*). Here, m is an integer number corresponding to an m-photon transition from the ground state to the first excited state (Fig. 1B). Figure 3A shows the evolution of the switching-current histogram as a function of the applied microwave power for the three-photon process. At low power values (–20 dBm, measured at the room temperature termination), the occupation probability of the first excited state is negligible and the switching histogram is unperturbed, corresponding to the escape from the ground state. When the applied power is increased, the first excited state starts to be populated. Then the histogram becomes doubly peaked (–17 dBm and –16 dBm), corresponding to tunneling from the first excited and ground states. The occupation probability of the ground and first excited state will become comparable (50% each) by further increasing the applied power. The escape from the first excited state is exponentially faster and dominates. Therefore, the switching current distribution is again single peaked at –14 dBm.

The escape rates derived from the switching probabilities are shown for various microwave

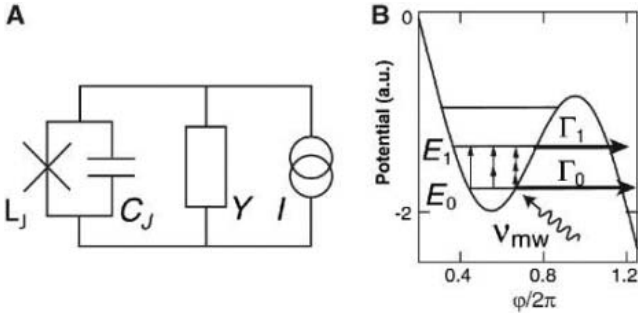

Fig. 1. Circuit diagram and energy levels. (**A**) Equivalent circuit diagram of a current-biased JJ. The Josephson inductance L_J and the junction capacitance C_J form an anharmonic oscillator. The damping of the oscillator caused by dissipation is described by the shunting admittance Y. It includes dissipation effects both intrinsic to the junction and caused by the electromagnetic environment connected through the biasing leads to the junction. (**B**) Energy levels in the cubic potential of the current-biased JJ. Microwave-induced transitions from the ground state (E_0) to the first excited state (E_1) are shown for the one-, two-, and three-photon processes. The phase tunnels out of the potential well at a rate Γ_0 from the ground state, and at a rate $\Gamma_1 \gg \Gamma_0$ from the first excited state that is populated by resonant microwave radiation. a.u., arbitrary units.

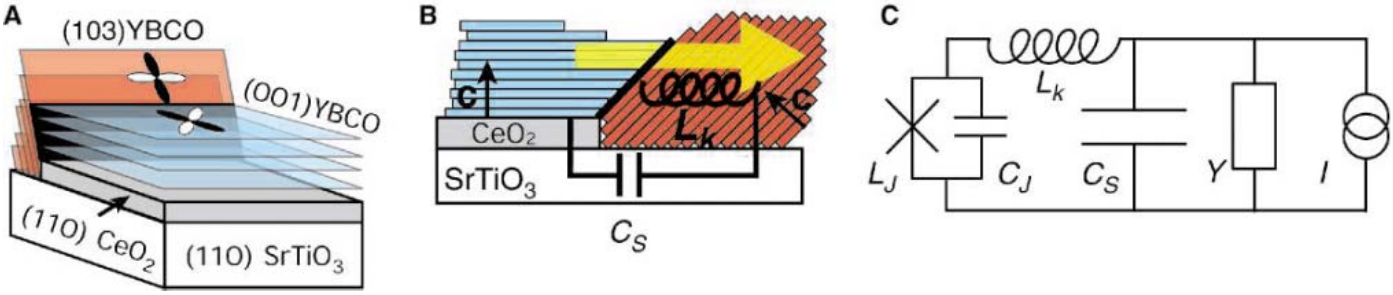

Fig. 2. Sample and extended circuit diagram. (**A**) Sketch of the bi-epitaxial YBCO junction. The JJ is formed at the boundary (black area) between (001) YBCO and (103) YBCO electrodes. A lobe of the superconducting order parameter in one electrode is facing a node of the order parameter in the other electrode. The normal state resistance of the JJ extracted from the current voltage characteristic is 450 ohms. The width w of the junction is 4 μm and the thickness t is 120 nm. The 4-μm-wide electrodes on both sides of the grain boundary extend over a length of 10 μm. 100-μm-wide leads then connect the electrodes to the bonding pads. (**B**) Cross section of the grain boundary junction. It illustrates the stray capacitance and kinetic inductance of the JJ. The large dielectric constant of the STO substrate at low temperature ($\varepsilon_r > 10{,}000$) results in a stray capacitance C_S between the electrodes dominating the total capacitance of the system. The large London penetration depth λ_L in the c-axis direction of the YBCO results in a large kinetic inductance L_k of one of the electrodes, where the bias current (yellow arrow) is partially flowing in the c direction. (**C**) Extended circuit diagram for the JJ, including the stray capacitance and kinetic inductance. The stray capacitance C_S can be considered in parallel to the junction through the electrode kinetic inductance L_k. For $C_S \gg C_J$, the stray inductance L_k adds up to the Josephson inductance L_J, resulting in an energy-level separation between the first excited state and ground state of our system given by the relation $h\nu_{01} = (h/2\pi)[(L_J + L_k)C_S]^{-1/2}$.

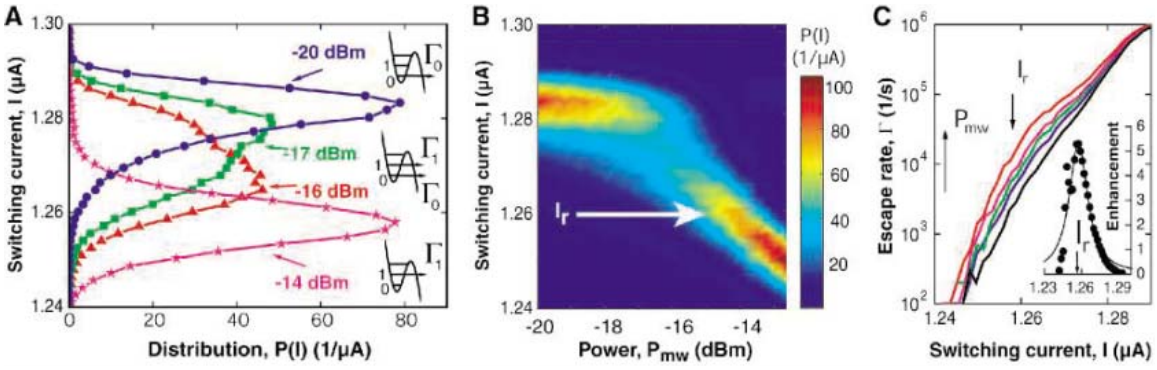

Fig. 3. Spectroscopy data. (**A**) Measured switching current probability distribution $P(I)$ in presence of microwaves at a frequency ν_{mw} = 850 MHz and temperature T = 15 mK. The applied power at the room temperature termination varies from −20 to −14 dBm. (**B**) Density plot of the measured $P(I)$ distributions as a function of the applied microwave power for ν_{mw} = 850 MHz and T = 15 mK. The resonance current I_r, where a resonant transition from the ground state to the first excited state occurs, is indicated by the arrow. (**C**) Escape rate extracted from the measured $P(I)$ distributions shown in Fig. 3A for increasing microwave power from −20 to −16 dBm (upward-pointing arrow). The escape rate is enhanced at the resonance current because of population of the first excited state. The enhancement of the escape rate $[\Gamma(P_{mw}) - \Gamma(0)]/\Gamma(0)$ at P_{mw} = −17 dBm is shown (solid circles) in the inset. The solid line is a fit to a Lorentzian. From the full width at half maximum, we extract a width in frequency $\delta\nu \approx 21$ MHz, yielding a quality factor $Q = \nu_{mw}/\delta\nu \approx 40$. The resonance current I_r is indicated by the downward-pointing arrows.

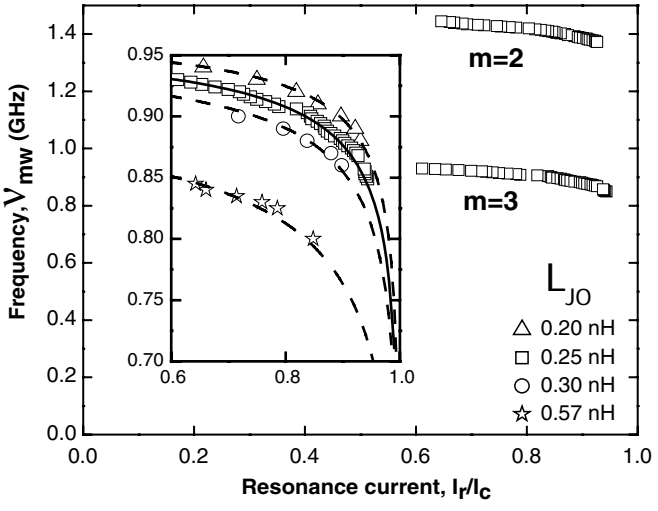

Fig. 4. Microwave frequency ν_{mw} versus normalized resonance current I_r/I_c. The two branches correspond to the two-photon (m = 2) and three-photon (m = 3) transitions. The ratio between the two- and three-photon frequencies is 3/2 within 3% for the measured range of resonant currents. The inset shows the measured microwave frequency versus normalized resonant current for the three-photon transition (m = 3) at four different Josephson inductances L_{J0} (symbols). The solid line is a fit to the experimental data with L_{J0} = 0.25 nH according to the resonance condition $6\pi\nu_{mw}(I_r) = C_S^{-1/2}[L_k + \varphi_o[1 - (I_r/I_c)^2]^{-1/2}/2\pi I_c]^{-1/2}$. The resulting fitting parameters L_k = 1.7 nH and C_S = 1.6 pF are used to calculate the frequency versus resonance current dependence for the other three values of the Josephson inductances (dashed lines). Experimentally, the families of values are obtained by varying the Josephson current by a magnetic field.

powers (Fig. 3C). A pronounced bump appears when the power is increased, indicating resonant activation of the excited level. The enhancement of the escape rate can be obtained by subtracting the unperturbed rate from the escape rate in the presence of microwaves (Fig. 3C, inset). The curve can be fitted by a Lorentzian, which indicates a resonant activation mechanism induced by level quantization. Moreover, the width of the enhancement curve is a measure of the quality factor Q. In the specific case of Fig. 3C, we get a Q value of the order of 40, which is comparable with the best results obtained in LTS junctions (*29*). However, much higher values for Q have been measured in LTS JJs by proper high-frequency engineering of the junction environment (*30*). The value of the quality factor demonstrates clearly that the dissipation mechanisms, including the one caused by low-energy excitations, do not prevent the observation of level quantization in the washboard potential.

The resonant bias current I_r, corresponding to the escape of the phase enhanced by microwaves (Fig. 3, B and C, arrow), is shown in Fig. 4 for various applied microwave frequencies. We can clearly distinguish two branches, corresponding to the two-photon (m = 2) and three-photon (m = 3) transitions from the ground state to the first excited state. The applicability of the equivalent circuit of Fig. 2C can be demonstrated by varying the Josephson inductance at zero bias, $L_{J0} = \varphi_0/2\pi I_c$, by an external magnetic field and measuring the bias current dependence of the energy-level separation ν_{01} for the three-photon process. The Josephson inductance L_{J0} at zero bias was determined from the unperturbed switching current histograms. From the fit of the data with L_{J0} = 0.25 nH (solid line in the inset of Fig. 4), we obtain the two fitting parameters: C_S = 1.6 pF and L_k = 1.7 nH. The dashed lines in the inset of Fig. 4 are the calculated current dependences of the three-photon transition frequencies from the ground to the first excited state using the same fitting parameters, C_S and L_k. The agreement between the experimental data and the calculated curves is excellent, indicating that the circuit of Fig. 2C describes well the Josephson quantum dynamics of our system. The fitted kinetic inductance agrees well with an estimate from geometry, $L_k = \mu_o\lambda_L^2/wt$, where μ_o is the magnetic constant, w is the width, and t is the thickness of the electrode, assuming an electrode length L = 10 μm and a London penetration depth in the c-axis direction $\lambda_L \approx 6$ μm (*31*). The correction to the Josephson inductance due to the doubly degenerate ground state can be neglected because of the large value of the kinetic inductance (*22*).

One may ask why no m = 1 curve is seen. We attribute the fact that we do not observe the one-photon (m = 1) transition at $\nu_{01} \approx 2.6$ GHz to the strongly frequency-dependent coupling of microwaves to the sample caused by the high dielectric constant of the STO substrate. Indeed, for frequencies larger than 4 GHz, no microwaves could be coupled; moreover, the STO substrate acts as a dielectric resonator. Therefore, microwaves can couple to the junction only at certain frequencies determined by the geometric resonance condition of the dielectric resonator. Microwaves that do not match the resonance condition of the STO substrate will be reflected to a large extent. This

seems to be the case for the one-photon transition frequency ν_{01}. This fact is also confirmed by the large quality factor that we extract from the resonant activation measurements. From Q, we derive the total shunting impedance $1/\mathrm{Re}(Y) = 4700$ ohms of the junction. This is much larger than the expected shunt impedance for a current-biased JJ, which is approximately the typical wire impedance at microwave frequencies ≈100 ohms. In this sense, the STO dielectric resonator protects the junction from its environment at the characteristic transition frequency ν_{01}.

Even though with our experiment, we are not able to determine univocally the intrinsic dissipation of the Josephson element, we can extract a lower bound. Assuming that all dissipation comes from the Josephson element, we can calculate the intrinsic impedance $1/\mathrm{Re}(Y_{\mathrm{int}})$ in parallel with the Josephson inductance. According to the circuit of Fig. 2C, we have $1/\mathrm{Re}(Y_{\mathrm{int}}) = L_J^2/(L_J + L_S)^2\mathrm{Re}(Y) \approx 700$ ohms for the lowest value of the intrinsic impedance due to low-lying energy excitations. This result may open up the possibility for some kind of freezing mechanism for quasiparticles at very low temperature and/or the existence of a subdominant imaginary s-wave component of the order parameter inducing a gapped excitation spectrum. The observation of quantum tunneling, narrow width of excited states, and a large Q value support the notion of "quiet" qubits based on d-wave symmetry superconductor.

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Quantum Deconstruction of the Infrared Spectrum of CH_5^+

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We present two quantum calculations of the infrared spectrum of protonated methane (CH_5^+) using full-dimensional, ab initio–based potential energy and dipole moment surfaces. The calculated spectra compare well with a low-resolution experimental spectrum except below 1000 cm^{-1}, where the experimental spectrum shows no absorption. The present calculations find substantial absorption features below 1000 cm^{-1}, in qualitative agreement with earlier classical calculations of the spectrum. The major spectral bands are analyzed in terms of the molecular motions. Of particular interest is an intense feature at 200 cm^{-1}, which is due to an isomerization mode that connects two equivalent minima. Very recent high-resolution jet-cooled spectra in the CH stretch region (2825 to 3050 cm^{-1}) are also reported, and assignments of the band origins are made, based on the present quantum calculations.

The CH_5^+ cation was brought to the forefront of scientific interest by a range of experimental studies (*1*–*8*) and ab initio electronic structure calculations at the stationary points (*9*–*14*) that hinted at a very high degree of fluxionality owing to the unusual two-electron–three-center bonding. The large-amplitude motions displayed by CH_5^+, even in its ground state, have made spectral assignments challenging, as is evidenced by the unassigned spectrum of Oka and co-workers (*7*). Recently, a low-resolution laser-induced reaction (LIR) infrared (IR) action spectrum of CH_5^+ was reported by Asvany *et al.* (*1*). This spectrum was recorded at 110 K over a large spectral range, 540 to 3250 cm^{-1}. The LIR spectrum is a major step forward in unraveling the dynamics of this cation.

Until very recently, dynamical studies of CH_5^+ have been hampered by the lack of a full-dimensional potential energy surface (PES). Such surfaces have just appeared and have been used in a variety of classical and quantum diffusion Monte Carlo (DMC) calculations of the ground state of CH_5^+ and its isotopomers (*15*–*19*). Thus, dynamics and vibrational calculations before 2004 were carried out in a direct fashion, that is, calculating the potential and gradients "on the fly" (*20*–*23*). These pioneering calculations were done using fairly low-level density functional theory (DFT) calculations; nevertheless, they provided great insight into the fluxional nature of CH_5^+. Indeed classical, direct-dynamics DFT simulations of the IR spectrum were also reported in (*1*) at 50 and 300 K. The 300 K spectrum is in good qualitative agreement with experiment above 1000 cm^{-1}. Below 1000 cm^{-1}, intense absorption was seen in the classical spectrum but not in the experimental one, perhaps because of a lack of experimental sensitivity in that spectral region. However, it is well known that, except in the harmonic limit, classical spectra can differ substantially from quantum spectra because of the lack of quantization in the classical dynamics. Thus, while the agreement between the classical and LIR spectra above 1000 cm^{-1} was gratifying, the differences below 1000 cm^{-1} remain an open issue.

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Motivated by this new experimental spectrum, we undertook two quantum approaches to calculate and deconstruct the LIR spectrum using the best techniques available. In this work, we make use of a new (nonglobal), full-dimensional potential energy surface (*19*) based on the accurate coupled-cluster method [CCSD(T)] with the aug-cc-pVTZ basis and the previous MP2-based dipole moment surface (*15*). We refer to these potential and dipole moment surfaces as the CCSD(T)-MP2 surfaces. Even with these surfaces, "exact" quantum calculations of the IR spectrum are beyond reach because of the highly fluxional nature and the high dimensionality (12 internal degrees of freedom) of the CH_5^+ wave functions.

Two low-lying saddle points are the bottlenecks to the fluxional, isomerizing motion of CH_5^+. The structures and energies of the stationary points are depicted in Fig. 1. These two saddle points, and the 120 equivalent minima they connect, govern the short-time dynamics of the isomerization and, from well-known quantum time-energy relations, determine the IR spectrum under low resolution. Because our goal is to deconstruct the low-resolution LIR spectrum, we focus our quantum calculations on the minimum and these two saddle points. In one set of calculations, we perform double-harmonic (HO) calculations of the IR spectrum at these three stationary points, using the CCSD(T)-MP2 surfaces. We then weight the combined results by using the ground-state density obtained from a rigorous quantum DMC calculation (*24*). A second set of calculations was performed with the code MULTIMODE (MM), which uses variational configuration interaction methods to obtain vibrational energies and wave functions of polyatomic molecules. The code also uses an n-mode representation (nMR) of the potential that permits application to fairly large molecules (*25*). Properties such as the IR spectrum can be obtained with these wave functions; recently, this code and DMC calculations were used to stimulate the IR spectrum of $H_5O_2^+$ (*26*). In the present calculations, the single-reference version of MM is used with a four-mode representation of the potential to obtain the spectra. Higher level 5MR calculations of the vibrational eigenvalues were also performed to check the convergence of the 4MR calculations (*27*). The reference geometries for the calculations are the global minimum and the two saddle points, the same geometries used in the HO calculations, depicted in Fig. 1.

In Fig. 2, we present the stick spectra from the HO calculations and the MM calculations at the three stationary points, as well as a Gaussian convolution with full-width–half-maximum (FWHM) of 200 cm^{-1}. This width was chosen to approximate the resolution of the experimental spectrum. Both spectra have features that span the entire spectral range shown, but with no features in the 1800 to 2100 cm^{-1} range. There are quantitative differences between the spectra, with the MM spectrum showing more lines and spectral features somewhat red-shifted relative to HO spectra, as expected. In the case of the latter, each stick corresponds to a harmonic normal mode at the corresponding stationary point. For these plots, we only include the modes with real frequencies. Consequently, only 11 features are seen in the spectra at the C_{2v} and C_s(II) saddle points, because in these cases one of these frequencies becomes imaginary, whereas all 12 modes are used to construct the spectrum at the C_s(I) minimum.

These imaginary frequency modes appear as real excitations in the MM spectra. For example, at the C_{2v} saddle point reference geometry, the fundamental associated with the imaginary frequency mode is found at 200 cm^{-1} and has the greatest intensity of all the spectral lines in this spectrum. Comparison of the MM spectra at the three reference geometries shows that they are similar, especially those obtained using the C_{2v} and C_s(I) reference geometries. If these MM calculations were exact, the spectra from all three reference geometries would be identical. They are similar, but not the same, and one way to distinguish among them is to compare the zero-point energies with the exact one, obtained from DMC simulations. On the basis of this comparison (*27*), the C_{2v} reference geometry would be the preferred one. This might also be argued to be the best reference geometry because a grid centered there spans two equivalent minima and the C_s(II) saddle point. However, for comparison with experiment, we used the sum of the three MM spectra, weighted by the DMC populations at the corresponding reference geometry. Comparing the HO and MM spectra at the three stationary points, we note that there is also good overall agreement above 1000 cm^{-1}. As we noted previously (*16*), the two lowest frequency modes are very anharmonic, and differences below 1000 cm^{-1} reflect a breakdown of the HO approximation in this region.

Figure 3A shows a comparison of the calculated spectra with the experimental spectrum of Asvany *et al*. The MM and HO spectra are sums of the convoluted spectra shown in Fig. 2, weighted by the DMC ground-state density at the three stationary points. Because of the highly anharmonic nature of the low-frequency modes, the HO spectrum is only plotted for transitions above 900 cm^{-1}. There is very good agreement between the experimental and calculated spectra above 1000 cm^{-1}, with near quantitative agreement for the MM spectrum. At lower frequencies, intensity is seen both in the MM spectrum and in the HO spectra, plotted in Fig. 2A, that is not evident in the experimental one. The absence of these intense spectral features in the experiment appears to be due to the loss of sensitivity of

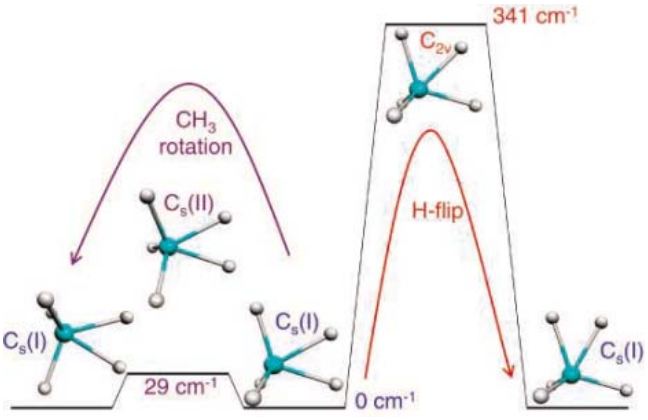


Fig. 1. Structures of CH_5^+ at the three stationary points on the potential. Energies provide the relative energies on the CCSD(T) surface.

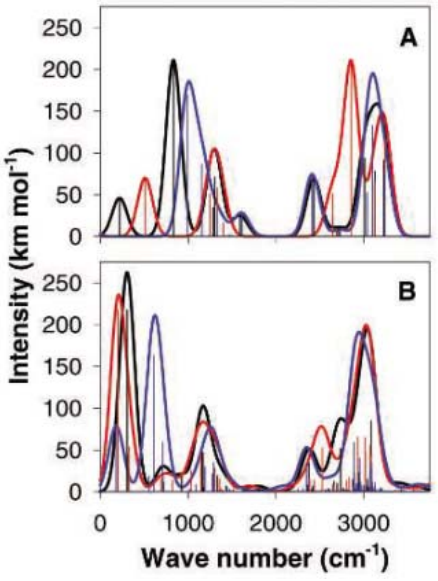


Fig. 2. Stick and Gaussian convoluted (FWHM = 200 cm^{-1}) spectra for CH_5^+ from (**A**) the double-harmonic calculations at the C_s(I) (black), C_{2v} (red), and C_s(II) (blue) stationary points and from (**B**) the MULTIMODE calculations, using the three stationary points as reference geometries. For all of these calculations, the reported intensities for the stick spectra are given in units of km mol^{-1}.

the experimental action spectrum as discussed in detail in (*1*). Interestingly, the present quantum spectra agree qualitatively with the classical one given in (*1*) in that both predict intense spectral features in this low-frequency regime. The DMC-weighted spectra agree better with experiment than any single spectrum shown in Fig. 2. This is particularly relevant for the HO spectrum and reflects the importance of all three stationary points in capturing the spectroscopy (and dynamics) of this fluxional system.

Given the good agreement with the experimental spectrum, we can assign the prominent spectral features to specific vibrations with confidence. For this analysis, we focus on the C_{2v} reference geometry, which yields several prominent features in the convoluted calculated spectra, three of which line up very well with experiment. We analyze the harmonic modes and MM wave functions that correspond to these features. For the harmonic treatment, the analysis is straightforward. For the MM wave functions, we focus on the fundamentals that provided the leading contributions to the intense bands in each spectral region. From this analysis, we find that only one or two modes provided the leading contributions to the intensity in the four regions, labeled a to d in Fig. 3A. These are depicted with the harmonic frequencies and MM energies of the corresponding major bright eigenstates in Table 1, in effect representing a quantum deconstruction of this spectrum. Feature a, the most intense one, corresponds to the imaginary frequency isomerization mode at the C_{2v} saddle point. Displacement in this coordinate brings CH_5^+ close to its geometry at a C_s(I) minimum (Table 1). Feature b reflects two modes of roughly equal intensity in the HO spectrum. These modes can be best thought of as bending or rocking motions of H_A-C-H_C and H_D-C-H_E. Finally, the large peak at high frequency (c and d) and the smaller shoulder on the red side of this feature result from CH stretching vibrations. The descriptions of all six of these modes will change if one of the other two stationary points is considered. These reflect differences in the overall symmetry of the ion; the qualitative picture, however, remains the same.

This theoretical deconstruction clearly works well in comparison with the low-resolution LIR spectra. We can also test predictions against high-resolution direct absorption spectra of jet-cooled CH_5^+ in the 2825 to 3050 cm^{-1} region that we obtained recently (*28*). Because the present theoretical study does not include rotational structure, we compare a 10 cm^{-1} convolution of both experimental and theoretical (DMC-weighted MM) spectra in Fig. 3B. Despite the simplicity of the approach, there is a very good correlation between the two largest peaks in the convoluted experimental spectrum and the accumulation of transitions near 3010 and 3075 cm^{-1} in the MM spectrum when we shift the MM spectrum by 58 cm^{-1}. The size of this shift is well within the uncertainties of the present calculations, which contain errors that arise from both the PES and the vibrational calculations. These features can be assigned to two normal-mode CH-stretch fundamentals of the CH_3^+ subunit. This simple vibrational assignment may seem surprising for such a fluxional molecule. However, if one considers a HO treatment at the three stationary points, the two highest frequency modes all correspond to stretches of the CH_3^+ subunit, with the corresponding frequencies lying in tight windows from 3097 to 3128 cm^{-1} and 3226 to 3237 cm^{-1}, respectively. Therefore, these highest frequencies appear not to be affected by the lower frequency fluxional motions of CH_5^+.

We find these comparisons extremely encouraging, but much still remains to be learned

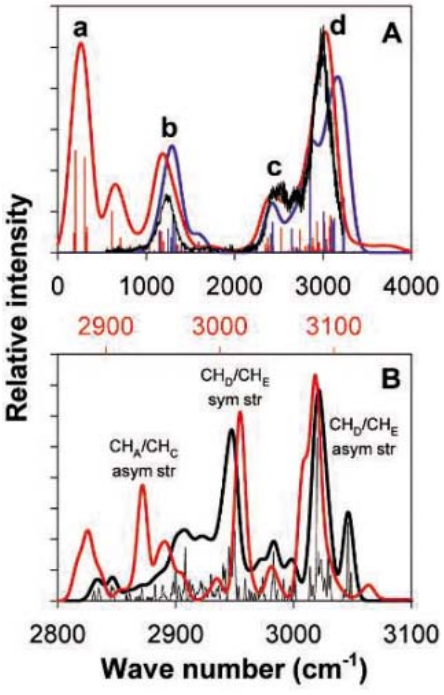
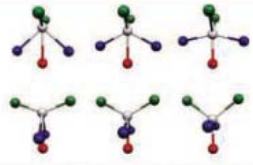
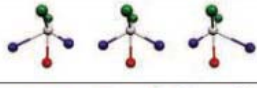
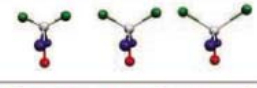
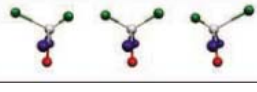


Fig. 3. Comparison of the experimental (**A**) LIR spectrum and (**B**) convoluted high-resolution spectrum and the calculated spectra of CH_5^+, with the experimental spectra plotted in black, the MULTIMODE spectra in red, and the harmonic spectrum in blue. The calculated spectra are obtained by weighting the spectra obtained at each stationary point by the probability amplitude at the stationary points and summing the spectra. For (A), the stick spectra are convoluted by a Gaussian function with FWHM = 200 cm^{-1}; in (B), the experimental spectrum is convoluted to a 1 cm^{-1} (thin line) and 10 cm^{-1} (thick line) FWHM, whereas the calculated spectrum uses a FWHM of 10 cm^{-1} and has been shifted by 58 cm^{-1} relative to the experimental spectrum, as indicated by the scaling on the top of the graph.

Table 1. Normal modes and frequencies (cm^{-1}) at the C_{2v} saddle point that contribute intensity to features a to d in Fig. 3A. Numbers in parentheses are the 5MR MULTIMODE energies (*27*) of the major eigenstate of these features obtained from the calculation at the C_{2v} reference geometry. We have used red, blue, and green to differentiate the hydrogen atoms, where atoms A and C are blue, atom B is red, and atoms D and E are green.

Feature*	Frequency†	Motion	Normal Mode Displacements‡
a	688i (175)	H_B flip	
b	1246 (1116)	H_A-C-H_C bend/ H_D-C-H_E bend	
b	1328 (1293)	H_A-C-H_C rock/ H_D-C-H_E rock	
c	2854 (2468§) (2888‖)	CH_A/CH_C asymmetric stretch	
d	3121 (2983)	CH_D/CH_E symmetric stretch	
d	3237 (3067)	CH_D/CH_E asymmetric stretch	

*See Fig. 3A. †Harmonic (and MULTIMODE) frequencies. ‡Pictorial depiction of the displacements. §Minor contributor to feature c, characterized as the fundamental in the CH_B stretch. ‖Mainly CH_A/CH_C asymmetric stretch, but a mixed state.

about CH_5^+ from its high-resolution spectra and accompanying rotational structure. Indeed, this is where subtle but revealing effects of the end-over-end tumbling, nuclear spin statistics, and tunneling splittings will be addressed that can not be accurately treated in the present vibrational framework (*29*, *30*). The detailed interpretation of the high-resolution spectrum of CH_5^+ and its isotopomers will clearly provide interesting opportunities for further theoretical and experimental challenges in this elusively fluxional species. Extensions of the present work to include deuterated analogs of CH_5^+ (*31*) and to probe the effects of rotations are currently under way.

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Planktonic Foraminifera of the California Current Reflect 20th-Century Warming

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It is currently unclear whether observed pelagic ecosystem responses to ocean warming, such as a mid-1970s change in the eastern North Pacific, depart from typical ocean variability. We report variations in planktonic foraminifera from varved sediments off southern California spanning the past 1400 years. Increasing abundances of tropical/subtropical species throughout the 20th century reflect a warming trend superimposed on decadal-scale fluctuations. Decreasing abundances of temperate/subpolar species in the late 20th century indicate a deep, penetrative warming not observed in previous centuries. These results imply that 20th-century warming, apparently anthropogenic, has already affected lower trophic levels of the California Current.

Records of various marine populations reveal that large declines in some marine algae, zooplankton, fish, and seabirds in the California Current in the late 20th century were linked to widespread ecosystem changes throughout the North Pacific in the mid-1970s (*1*–*8*). The associated change in environmental conditions resembled a sustained El Niño–like state, whereby greater cyclonic activity of the atmospheric Aleutian Low Pressure System was accompanied by warming in the eastern North Pacific (*1*–*14*). The origin of this ecosystem "regime shift" (*15*, *16*) has been a source of debate since its detection. On one hand, changes in marine populations are often attributed to decadal-scale fluctuations in ocean-atmosphere conditions that are characterized by the Pacific Decadal Oscillation (PDO) (*1*). On the other hand, the ecosystem shift could reflect penetration of a greenhouse gas–induced warming in the global ocean (*17*–*19*) that exceeded a threshold of natural variability. A major difficulty with attribution of cause is the short length of most time series of climate and ecosystem variability. The debate is further complicated by the fact that variations in many marine populations could result directly from other anthropogenic influences (such as habitat disturbance or fishing) and/or indirectly by trophic cascades. It is therefore difficult to distinguish threshold effects of a warming trend on marine populations from decadal-scale variability or other anthropogenic influences.

We present paleoceanographic evidence to show that populations of planktonic foraminifera in the California Current were strongly affected by a 20th-century warming trend. Planktonic foraminifera have been used extensively in paleoceanographic studies. They function at a low trophic level and their species-specific sensitivities to preferred hydrographic conditions link their temporal variations to changes in

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climate and primary productivity, with little evidence for controls of these assemblages by higher trophic levels (*20–29*). Our analysis builds on previous studies of variations in foraminiferal abundances in Santa Barbara Basin (SBB) sediments across El Niño and stadial/interstadial events (*20–22*) as well as studies of species-specific preferred habitats near the SBB (*22–28*). Although the SBB lies within an upwelling environment, regional- and basin-scale processes are considered more influential than high-frequency, local processes (*3*, *4*, *12–14*). The major interannual, decadal, and secular variations observed in sea surface temperature (SST) and zooplankton abundance at or near the SBB clearly follow the same patterns of variability observed coherently throughout the California Current (*3*, *4*, *12–14*, *30*). Thus, foraminifera preserved in SBB sediments provide a rare opportunity to compare 20th-century marine ecosystem conditions with those from previous centuries.

A continuous high-resolution record from SBB sediments results from high sedimentation rates and the regular occurrence of anoxic bottom waters, which inhibit bioturbation. Thus, seasonal alternations in the deposition of lithogenic and biogenic particles result in well-defined annual laminae that can be counted visually to develop a reliable chronology (*31*).

A principal components analysis (PCA) of the temporal variations in foraminiferal abundance from SBB sediments collected with a Soutar box corer in 2001 captures two main patterns of variability in the most abundant species over nearly 300 years (Fig. 1). The first principal component (PC1) involves a substantial 20th-century increase in the abundance of species of primarily tropical and subtropical affinities, along with a decrease in the abundance of *Neogloboquadrina pachyderma* (sin.), a species with subpolar to polar affinity. The second pattern (PC2) involves species with known temperate to polar affinities. The amplitudes of these two PCs covary on multiannual to decadal time scales ($P < 0.001$) until about 1959, when they begin to diverge (*32*). Postdepositional dissolution of tests cannot explain these patterns because species with both high and low resistance to dissolution have opposite loadings on the PCs (Fig. 2). Furthermore, comparing the amplitudes of the PCs with the averaged abundance of the same species constituting these PCs from separate SBB box cores taken in different years shows that the main temporal patterns are found in all cores and are detectable by different analytical approaches (Fig. 3) (*32*).

The temporal variability of PC1 reflects the principal multiannual to secular changes in SST over the past century (Fig. 3). This connection is not surprising because many of the tropical and subtropical species have symbiotic algae and favor environments with different combinations of higher SSTs, deeper thermoclines, and accompanying higher light levels (*22–27*). Therefore, anomalous near-surface warming and stratification, particularly in summer and fall, would expand the duration and extent of these species' preferred habitats and, consequently, their fluxes to the sediment (*22–27*). The association of *Globigerina bulloides* with PC1 is unexpected because it is typically associated with upwelling and/or conditions of high productivity. However, for *G. bulloides*, a threshold of unfavorable productivity can be reached during strong springtime upwelling in the nearby San Pedro Basin (*23*). In the SBB, the greatest fluxes of *G. bulloides* occur in spring of an anomalously warm year (e.g., 1997) and, more typically, in summer (*22*, *25*). Thus, the

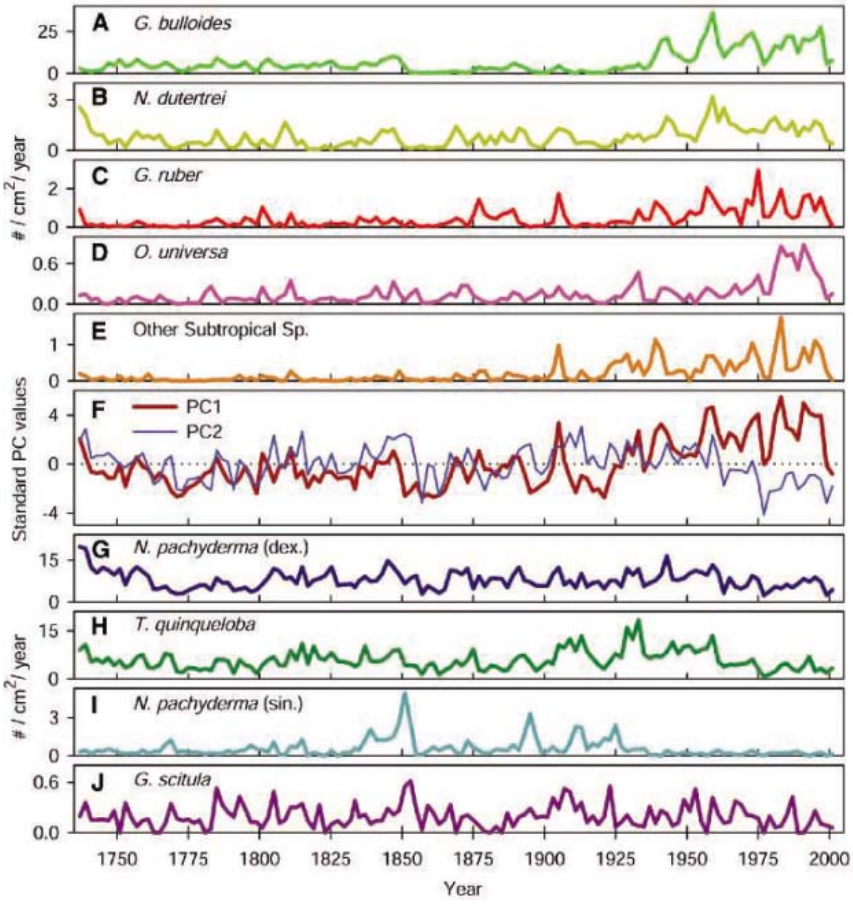

Fig. 1. Fluxes of planktonic foraminifera in Santa Barbara Basin (SBB) sediments from box core BC3001. (**A** to **E**) Taxa illustrating a significant trend ($P < 0.0001$ for each species) toward increasing abundances in the 20th century: (A) *G. bulloides*, (B) *N. dutertrei*, (C) *Globigerinoides ruber*, (D) *O. universa*, and (E) other subtropical species. (**G** to **J**) Species showing no temporal trend: (G) *N. pachyderma* (dex.), (H) *T. quinqueloba*, (I) *N. pachyderma* (sin.), and (J) *Globorotalia scitula*. (**F**) Temporal amplitudes of the first two principal components of the log-normalized time series of these species' abundances. PC1 and PC2 explain 40% and 21% of the total variance, respectively. Species loadings on PC1 and PC2 are shown in Fig. 2. "Other subtropical species" comprises the combined abundances of *Globigerinella calida*, *Globoturborotalita rubescens*, *Globigerinita glutinata*, *Globigerinella siphonifera*, and *Globigerinella digitata*, each of which occurred too infrequently to include individuality.

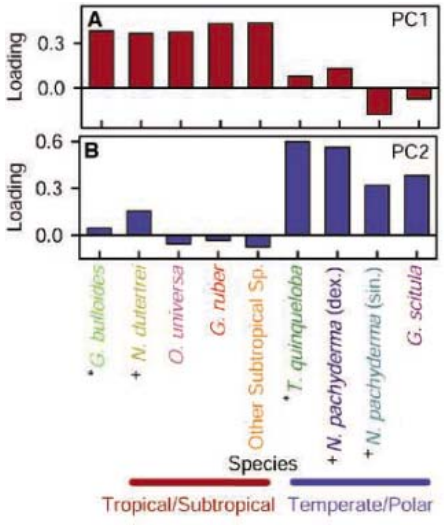

Fig. 2. Species loadings on PC1 and PC2, together with biogeographic affinities and dissolution susceptibility. Note that both species with high resistance to dissolution (+) and species with greater susceptibility to dissolution (*) have a range of opposing loadings on the two PCs.

association of *G. bulloides* with PC1 apparently reflects a preference for enhanced near-surface stratification during conditions of shoaling of isotherms (perhaps because prey would be more concentrated under these conditions than with a strictly isothermal water column). Accordingly, we interpret PC1 as the foraminiferal response to anomalous near-surface temperatures that modify stratification across the annual cycle of shoaling and deepening of isotherms.

The abundances of the deeper dwelling species that constitute PC2 generally increase with shallower isotherms and a cooler water column in this region of the California Current (*22*–*28*). However, there is also evidence that a strongly isothermal water column and very high productivity can be unfavorable for several of these species (*22*–*24*). Thus, their optimal environmental conditions would include some stratification, but less than for *G. bulloides* or other species associated with PC1. Accordingly, we interpret the time series of PC2 as primarily reflecting subsurface thermal adjustments to local and basin-wide wind fields and heat flux.

The covariation of PC1 and PC2 for much of the past few hundred years preceding the late 20th century indicates that some near-surface warming in the eastern Pacific can result in favorable environmental conditions for most species. Fluxes of species associated with PC1 would increase during late summer and fall, whereas species associated with PC2 (and *G. bulloides*) would generally increase during winter, spring, and summertime upwelling events. In addition, there may also be an increase in upwelling favorable winds during warm periods, because this has been observed during stadial events (*20*) and the late–20th-century warming (*12*, *13*, *33*). Nonetheless, upper ocean heat content has strongly increased in the late 20th century because the effect of atmospheric warming overwhelms the potential cooling effect of wind-induced shoaling of isotherms (*12*–*14*). Fluxes of species associated with PC2 decreased in the late 20th century as the deep, penetrative warming passed a threshold of optimum stratification, unlike prior warming events.

The obvious increases in abundance of several taxa through the 20th century (Fig. 1) can be placed into better perspective by comparing equivalent size fractions of *G. bulloides*, *Orbulina universa*, and *Neogloboquadrina dutertrei* from the box core records with those from a longer Kasten core record over the past 1400 or 1000 years (Fig. 4). The elevated abundance of *G. bulloides* in the 20th century is unique in comparison with any prior point over the past 1000 years. The sustained high abundance of *O. universa* after the mid-1970s is also particularly unusual. The 20th-century increases in *N. dutertrei* are moderate, relative to both previous centuries and the previous 1400 years. The unprecedented abundance maxima in two of three species examined shows that the foraminiferal fluxes in the late 20th century are not simply an extreme form of common decadal-scale variability.

The combination of persistently higher fluxes of tropical/subtropical species and higher maximum fluxes in the 20th century indicates that background climatic conditions may serve to amplify the effect of El Niño variability, and to diminish the effect of La Niña variability, on marine populations in the California Current. Although there is no evidence for a permanent shift in the duration, magnitude, or frequency of the El Niño–Southern Oscillation in the past several centuries (*34*), the greatest peaks in abundance of most species associated with PC1 coincide with the largest and most extended El Niño events observed in the California Current with instrumental records (Figs. 1 and 3). Also, the strong La Niña event of 1999 marks one of the coolest periods observed in many instrumental records within the past 55 years (*6*). However, unlike cool periods of previous centuries, the subpolar species *N. pachyderma* (sin.) did not increase in abundance; this species has been nearly absent for 70 years.

Visual inspection of PC1 indicates that the secular trend began around 1925, a time that matches the rise in regional and global SSTs (Fig. 3) (*35*). In models, ocean warming occurs in the early 20th century in response to the accumulation of greenhouse gases, but relatively deep mixing in most regions diffuses the warming throughout the water column to a magnitude that is less than background variability (*19*). The increase in PC2 along with PC1 indicates that increasing SSTs in the early 20th century were accompanied by relatively shallow isotherms, which would result in a stronger thermal gradient. A more stratified water column would inhibit deep mixing and concentrate the early expression of any greenhouse gas–induced warming in the near-surface, which in turn might explain the strong involvement of

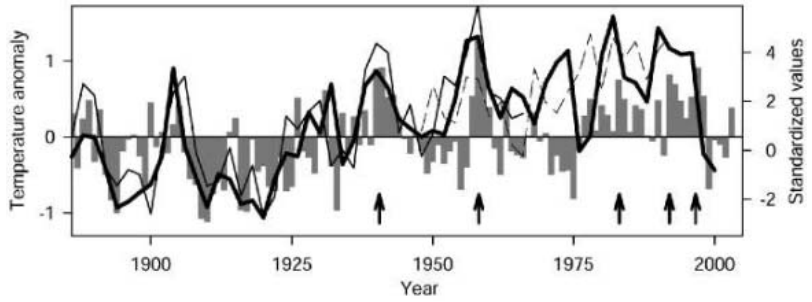

Fig. 3. Comparison of PC1 (bold solid line) with the SST record from the updated Kaplan reconstruction for the 5° × 5° grid centered at 122.5°W, 32.5°N (vertical bars) in the California Current near the SBB. PC1 is correlated with variations in SST from comparable 2-year averages of SSTs ($r^2 = 0.33$; $P < 0.001$). Arrows indicate strong El Niño events in the California Current. Also shown is the agreement of foraminiferal variations from PC1 (core BC3001) with those from two other cores in the SBB. Thin dashed line illustrates variations in averaged abundance of the same species loaded on PC1 from a core taken in 1992 and analyzed in this study. Thin solid line illustrates average of the principal species loaded on PC1 (*G. bulloides*, *N. dutertrei*, *G. ruber*, *O. universa*, and the combination of *G. calida* and *G. siphonifera*) from a core taken in 1969 and analyzed by A. Soutar and W. Berger.

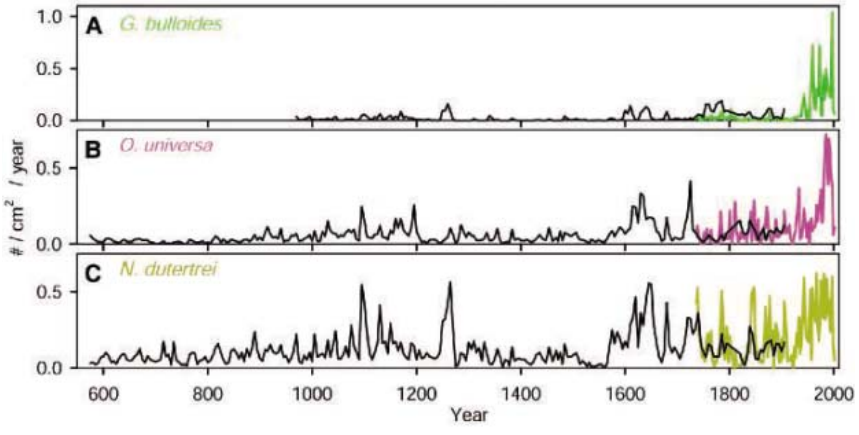

Fig. 4. Comparison of abundances of (**A**) *G. bulloides*, (**B**) *O. universa*, and (**C**) *N. dutertrei* in the 300- to 500-μm size fraction from 5-year sampling intervals in Kasten core sediments with abundances of the same species and size fractions from 2-year sampling intervals of box core sediments. The record in (A) is shorter because this species was not enumerated from the earliest strata.

the California Current region with the average warming trend in the global ocean (*35*, *36*). Our findings point to the possibility that anthropogenic warming has affected marine populations since the early 20th century, although only the ocean warming of the late 20th century has been confidently attributed to the accumulation of greenhouse gases (*17*–*19*).

Probably the most distinctive change in the foraminiferal record is the divergence in the time series of PC2 from the trend in PC1 that begins around 1960 and denotes a deeper penetration of the near-surface warming. This divergence reaches a maximum after the mid-1970s, coinciding with the well-documented change in climate and ecosystem throughout the North Pacific (*1*–*14*). The changes in foraminifera parallel decreases in the abundance of many taxa of algae, zooplankton, fish, and seabirds associated with temperate environments together with increases in many other tropical and subtropical taxa in the California Current (*1*–*7*). A recent study indicates that nonlinear biological responses to linear fluctuations in the physical environment play an important role in the ecosystem "regime shift" of the mid-1970s (*16*). Although it might be true that the foraminiferal response to SST and hydrography is also nonlinear (e.g., the response to different combinations of SST and thermocline structure), the divergence of the PCs in recent decades indicates that the trend in ocean heat content can also play an important role in the variations of some pelagic organisms.

The long-term warming trend described here helps to clarify how the mid-1970s regime shift in the North Pacific may be associated with atmospherically driven warming. It is well known that ocean changes since the mid-1970s are linked to an intensification of the atmospheric Aleutian Low Pressure System, which was partially driven by tropical SSTs (*9*–*11*). Atmospheric indices and tree ring–based reconstructions of the PDO indicate that the intensified Aleutian Low since the mid-1970s is the most persistent on record (*1*, *9*, *37*, *38*). More important, coral records indicate that the elevated tropical SSTs that drive cyclonic activity exceed prior decadal variability and were likely forced by greenhouse gases (*11*, *34*, *39*). Thus, although variations in the Aleutian Low are a component of natural variability, the late 20th century experienced unusual tropical forcing as well as increased atmosphere-driven heat flux to the ocean.

Foraminifera provide one of the clearest examples of a direct influence of an ocean warming trend on marine ecosystems because (i) their variability is more clearly related to hydrographic conditions than to trophic cascades resulting from anthropogenic activities occurring in the 20th century, (ii) a consistent time series of observations can be extended back hundreds of years, and (iii) the California Current region is strongly related to the average warming trend in the global ocean (*35*). Our results indicate that the variability of foraminifera in the California Current in the 20th century is linked to variations in SST and is atypical of the preceding millennium. Given that the trend in global SSTs has been attributed to increases in greenhouse gases in the atmosphere (*17*–*19*), it follows that the best explanation for this ecosystem aberration is anthropogenic warming that has passed a threshold of natural variability. As the warming of the ocean and atmosphere is likely to continue into the foreseeable future, the atypical state of the ocean over the period of most scientific observations must also be borne in mind for effective monitoring and management of living marine resources.

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31. See supporting material on *Science* Online.
32. PC1 and PC2 are uncorrelated (orthogonal) over the length of the whole time series, which is a criterion of any PCA. Similar correlations and patterns of variability are maintained when either of the time series are constructed on the basis of averages of log-normalized abundances of the same species rather than the PCs (Fig. 3) (*24*). The correlation between PC2 and PC1 ($r^2 = 0.11$) over the years 1736 to 1959 is higher when PC1 is lagged by one term ($r^2 = 0.14$; 2 years) or two terms ($r^2 = 0.19$; 4 years). This lagged correlation may be a consequence of the PCA output or perhaps implies some feedback component in the physics affecting species associated with PC2 with respect to near-surface variability associated with PC1.
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36. The PDO is the leading principal component of SST anomalies in the North Pacific Ocean (poleward of 20°N) with the global average SST anomalies removed [(*1*); see also http://jisao.washington.edu/pdo/PDO.latest]. Thus, the PDO captures the dipole of thermal variability characterized by SST anomalies of opposite sign between the eastern Pacific and the central North Pacific, but not the SST trend. Empirical orthogonal function analysis of global SST anomalies shows that both the trend and PDO variability are strong sources of variability throughout the California Current (*35*).
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Variability in Nocturnal Nitrogen Oxide Processing and Its Role in Regional Air Quality

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Nitrogen oxides in the lower troposphere catalyze the photochemical production of ozone (O_3) pollution during the day but react to form nitric acid, oxidize hydrocarbons, and remove O_3 at night. A key nocturnal reaction is the heterogeneous hydrolysis of dinitrogen pentoxide, N_2O_5. We report aircraft measurements of NO_3 and N_2O_5, which show that the N_2O_5 uptake coefficient, $\gamma(N_2O_5)$, on aerosol particles is highly variable and depends strongly on aerosol composition, particularly sulfate content. The results have implications for the quantification of regional-scale O_3 production and suggest a stronger interaction between anthropogenic sulfur and nitrogen oxide emissions than previously recognized.

Photochemical ozone production in the lower troposphere depends critically on the concentration of NO_x (which is equal to the sum of NO and NO_2) (*1*). In sunlight, NO_x acts as a catalyst in cycles that produce O_3 while oxidizing volatile organic compounds (VOC). At night, when the photochemical cycles are inactive, NO_x enters a different pathway via the oxidation of NO_2 by O_3 to give the nitrate radical, NO_3 (*2*, *3*). The nocturnal nitrogen oxide reactions tend to counteract the daytime photochemical production of O_3; they remove NO_x and initiate the nocturnal oxidation of reactive VOC (e.g., higher alkenes, particularly biogenic compounds) (*4*). The nighttime pathway depletes the two main ingredients required for photochemical O_3 production (NO_x and VOC) while at the same time consuming, rather than producing, O_3.

A key step in nocturnal NO_x removal is the heterogeneous hydrolysis of dinitrogen pentoxide, N_2O_5.

$$NO_2 + O_3 \rightarrow NO_3 + O_2 \quad (1)$$

$$NO_3 + NO_2 \rightarrow N_2O_5 \quad (2a)$$

$$N_2O_5 \rightarrow NO_2 + NO_3 \quad (2b)$$

$$N_2O_5 + H_2O\ (\text{het}) \rightarrow 2HNO_3 \quad (3)$$

$$\text{Net: } 2NO_2 + O_3 + H_2O\ (\text{het}) \rightarrow 2HNO_3 + O_2 \quad (4)$$

Although reaction 3 is very slow in the gas phase, it can be rapid on aerosol particles as a heterogeneous process. Therefore, it has a substantial impact on the lifetime and abundance of NO_x (*3*, *5*).

In spite of its importance, relatively little is known about the actual efficiency of N_2O_5 hydrolysis in the nocturnal atmosphere. In this study, we provide direct experimental determinations of N_2O_5 uptake coefficients on the basis of in situ measurements of NO_3, N_2O_5, and related compounds from an aircraft platform (the NOAA P-3) as part of an air quality study in the northeast United States (*6*). The analysis constrains the rate of N_2O_5 hydrolysis in anthropogenic NO_x plumes from both urban sources and power plants. It shows that there can be considerable chemical processing of NO_x at night via N_2O_5 hydrolysis and, importantly, that this processing is highly variable and depends strongly on aerosol composition. Because the variability exceeds that suggested by parameterizations of $\gamma(N_2O_5)$ used in atmospheric models to date (*7*–*10*), these observations are pertinent to the understanding of NO_x processing and regional air quality and to global budgets of NO_x, O_3, and other oxidants.

A map of the northeast United States (Fig. 1) indicates the location of major NO_x sources. Overlaid is the flight track for the NOAA P-3 on 9 and 10 August 2004. This flight occurred mainly at night, with local sunset about 1 hour into the 8-hour flight. The map indicates three regions with distinctly different NO_3 and N_2O_5 chemistry. In region I (over Ohio and western Pennsylvania), there was relatively little NO_3 and N_2O_5 even though the ozone mixing ratios were sufficient to rapidly oxidize NO_2 via Eq. 1. There was no measurable NO in these air masses, so the reaction of NO_3 with NO also could not account for the small concentrations of NO_3 and N_2O_5. Over eastern Pennsylvania, New Jersey, and downwind of New York (regions II and III), mixing ratios of NO_3 and N_2O_5 were consistently large [peak values of 0.4 and 3.1 parts per billion by volume (ppbv), respectively] even though NO_2 and O_3 mixing ratios in these regions were similar to those in region I (*6*).

That the NO_3 and N_2O_5 concentrations were small relative to their source (i.e., reaction 1) in region I indicates that their sinks were rapid or that their steady-state lifetimes (*11*) were short. Equations 5 and 6 show the relationship of the steady-state lifetimes (τ_{SS}) to the actual first-order sink rate coefficients for NO_3 and N_2O_5, k_{NO3} and k_{N2O5} (*12*).

$$\tau_{SS}(NO_3) \equiv \frac{[NO_3]}{k_1[NO_2][O_3]} = \left(k_{NO_3} + K_{eq}[NO_2] \times k_{N_2O_5}\right)^{-1} \quad (5)$$

$$\tau_{SS}(N_2O_5) \equiv \frac{[N_2O_5]}{k_1[NO_2][O_3]} = \left(k_{N_2O_5} + \frac{k_{NO_3}}{K_{eq}[NO_2]}\right)^{-1} \quad (6)$$

Here, k_1 is the rate coefficient for reaction 1 ($NO_2 + O_3$) and K_{eq} is the temperature-dependent equilibrium constant for reaction 2. The unitless quantity $K_{eq}[NO_2]$, equal to the ratio of N_2O_5 to NO_3 at equilibrium, serves as a weighting factor that shifts in favor of N_2O_5 at large NO_2 concentration or low temperature. The validity of a steady-state analysis of NO_3 and N_2O_5 sinks for these data was verified with a chemical box model (*6*, *12*).

The lifetimes of NO_3 and N_2O_5 varied considerably between regions I and III (color code in Fig. 1). Equations 5 and 6 provide a means to determine whether this difference was due primarily to reactions of NO_3 or N_2O_5; a plot of $\tau_{ss}(NO_3)^{-1}$ against $K_{eq}[NO_2]$ gives k_{NO3} as the intercept and k_{N2O5} as the slope (Fig. 2 left). The slope of the fit to the data from region I shows clear evidence for a rapid sink for N_2O_5, with $k_{N2O5}^{-1} = 10$ min. Analysis of several different NO_x plumes within this region gave similar results. By contrast, the slope of a fit to the data from region III is indistinguishable from zero and gives a lower limit (2σ uncertainty in the fit) of $k_{N2O5}^{-1} > 23$ hours. Again, this behavior is typical of several different plumes analyzed in this region. The intercepts differ by less than a factor of two, with values for k_{NO3}^{-1} of a few tens of minutes in both air masses. This lifetime is consistent with the presence of unsaturated VOC (e.g., isoprene and anthropogenic alkenes measured from canister samples) in these air masses, although an accurate budget for gas phase sinks of NO_3 would have required measurements for a larger array of VOC. A similar analysis of the same two flight segments using Eq. 6 (Fig. 2 right) gives k_{NO3} and k_{N2O5} as the slope and intercept,

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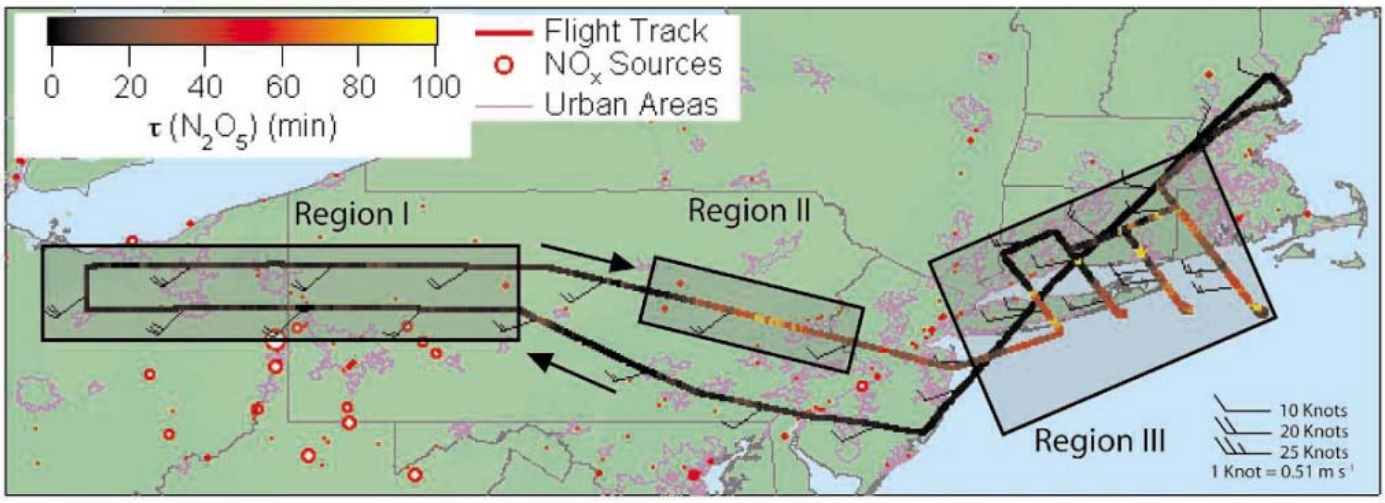

Fig. 1. P-3 flight track for 9 and 10 August 2004, color-coded according to the N_2O_5 lifetime, $\tau(N_2O_5)$. [This lifetime varied from <1 up to 250 min after sunset, but the color bar saturates at 100 min for clarity of contrast. Values of $\tau(N_2O_5)$ for N_2O_5 mixing ratios less than twice the 1-pptv detection limit have been arbitrarily set to zero.] NO_x point sources (sized according to emission rate) and urban areas are shown. Wind barbs give local wind speed and direction along the flight track.

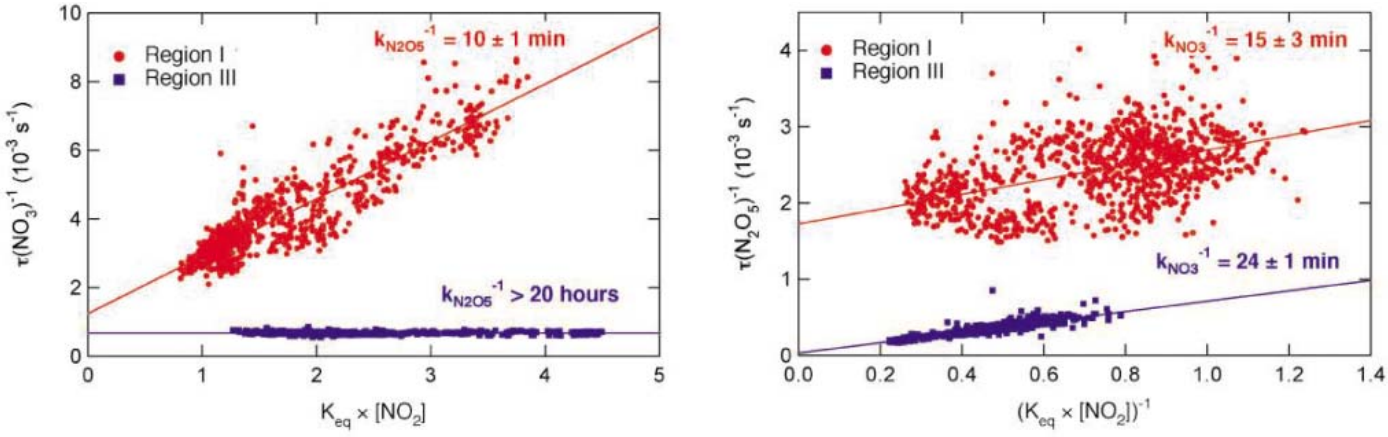

Fig. 2. Plots of $\tau_{ss}(NO_3)^{-1}$ versus $(K_{eq}[NO_2])$ **(left)** and $\tau_{ss}(N_2O_5)^{-1}$ versus $(K_{eq}[NO_2])^{-1}$ **(right)** for selected plumes from regions I and III of the flight in Fig. 1. The two plumes shown here were likely urban in origin (*6*), although air masses containing power plant plumes in both regions gave similar results. The solid lines are linear fits to the data, and the inverse of the slopes from each fit are given on the plot. The intercepts of each plot are equal to the slopes of the other plot to within the stated uncertainty on the figure, except for k_{N2O5}^{-1} in the upper figure, which is derived from the slope uncertainty as described in the text.

respectively, from a plot of $\tau_{ss}(N_2O_5)^{-1}$ against $(K_{eq}[NO_2])^{-1}$ and corroborates the result from Fig. 2 (left).

The measured aerosol surface area, in combination with k_{N2O5} from plots such as those in Fig. 2, gives a direct determination of the N_2O_5 uptake coefficient, $\gamma(N_2O_5)$ (*13*).

$$\gamma(N_2O_5) \approx \frac{4k_{N_2O_5}}{c_{mean}A} \qquad (7)$$

Here, c_{mean} is the mean molecular speed of N_2O_5 and A is the aerosol surface area density ($\mu m^2\ cm^{-3}$). Table 1 shows the average values of k_{NO3}^{-1}, k_{N2O5}^{-1}, aerosol surface area density, and $\gamma(N_2O_5)$ for the three regions marked in Fig. 1. The determined $\gamma(N_2O_5)$ in region I had an average value near 0.02, consistent with laboratory measurements on ammonium bisulfate particles (*14*–*17*), the largest component of the aerosol mass on this flight segment. However, in regions II and III, the $\gamma(N_2O_5)$ were at least an order of magnitude smaller; the values in Table 1 in these regions are conservative upper limits determined from the intercepts of the $\tau(N_2O_5)^{-1}$ versus $(K_{eq}[NO_2])^{-1}$ plots (Fig. 2 right). Values determined from the slopes of the $\tau(NO_3)^{-1}$ versus $K_{eq}[NO_2]$ plots (Fig. 2 left) are several times smaller.

The N_2O_5 loss rate coefficients in regions II and III were slow enough to be inconsistent with recent parameterizations from smog chamber measurements of the proposed, slow gas-phase homogeneous reaction of N_2O_5 with water vapor (*18*), which would give an N_2O_5 lifetime of about 2.5 hours (rather than the determined >6.5 hours) for the New York City plumes. If there is a small, homogeneous component to the N_2O_5 hydrolysis, then the upper limits to $\gamma(N_2O_5)$ in Table 1 for regions II and III are smaller.

The sharp change in $\gamma(N_2O_5)$ between the western and eastern flight legs was accompanied by a similarly sharp change in the aerosol fine particle composition (D_P < 1 μm, accounting for the majority of the particle mass and surface area) (Fig. 3). The largest observed difference between regions I and III was in sulfate aerosol mass loading. Because the organic content of the particles remained relatively constant, the sulfate/organic ratio also decreased considerably. The sulfate aerosol in region I was diffusely distributed rather than associated with the spatially narrow NO_x plumes sampled in this region. This observation, combined with meteorological analysis of the sampled air masses by the FLEXPART model (*19*) in region I, implies that the sulfate aerosol came from prior photochemical conversion of SO_2 to H_2SO_4 over the course of several days in the Midwest United States.

Table 1. Averaged actual (not steady-state) lifetimes of NO_3 and N_2O_5, aerosol surface area densities, and N_2O_5 uptake coefficients for different regions of the 9 and 10 August 2004 flight. The aerosol surface area densities have been corrected by factors from 1.1 to 1.65 to account for the hygroscopic growth of the particles between the sampled RH and the ambient RH. Uncertainties in k_{NO3}^{-1}, k_{N2O5}^{-1}, and aerosol surface are standard deviations from several determinations within each region.

Region	k_{NO3}^{-1} (min)	k_{N2O5}^{-1} (min)	Aerosol surface (μm^2 cm^{-3})	$\gamma(N_2O_5)$
I	13 ± 2	13 ± 2	1000 ± 140	0.017 ± 0.004
II	20 ± 2	>260	820 ± 80	<0.0010
III	31 ± 4	>400	340 ± 50	<0.0016

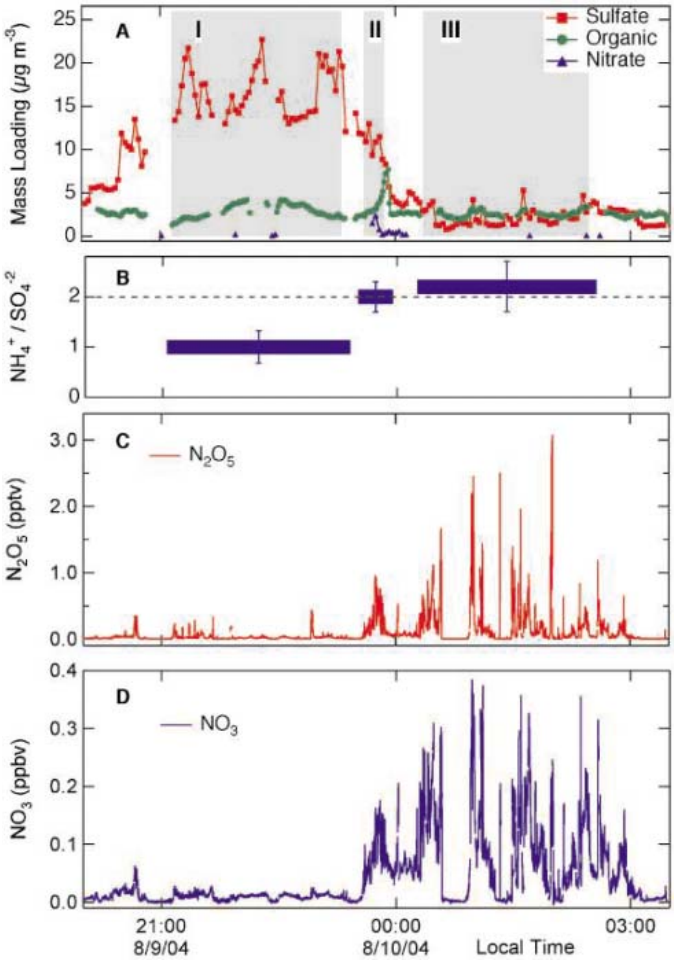

Fig. 3. (**A**) Aerosol sulfate, nitrate, and water-soluble organic carbon (WSOC, labeled "organic") mass loadings from the particle into liquid sampling (PILS) instrument for the 9 and 10 August flight for altitudes < 1.5 km. WSOC is in units of μg C m^{-3} and provides only a lower limit to the total organic mass. (**B**) Molar ratio of ammonium to sulfate from the same instrument. (**C** and **D**) Mixing ratios of N_2O_5 and NO_3, respectively. Local sunset occurred just before 20:00 local time.

The change in aerosol composition between regions I to III may have influenced $\gamma(N_2O_5)$ in several ways. First, the fraction of the total mass that was organic increased on the eastern leg. Laboratory measurements have shown small values for $\gamma(N_2O_5)$ on some pure organic substrates (*20*) and reductions in $\gamma(N_2O_5)$ upon addition of organic coatings to particles (*21*, *22*). The majority of particles sampled during the New England Air Quality Study–Intercontinental Transport and Transformation (NEAQS-ITCT) were internal mixtures of sulfate and organic compounds (*23*). Second, the apparent aerosol acidity also decreased on the eastern leg, as shown by the time series of the average NH_4^+/SO_4^{-2} molar ratio for each region (Fig. 3B). Acidic particles ($NH_4^+/SO_4^{-2} < 2$) tend to exclude NO_3^-, and laboratory studies have shown that NO_3^- inhibits N_2O_5 uptake (*14*, *24*). This effect may explain why $\gamma(N_2O_5)$ is small in region II, where the only measurable particulate NO_3^- was observed (Fig. 3). Lastly, the change from ammonium bisulfate to ammonium sulfate aerosol between regions I to III may have changed the relative humidity (RH) range over which the particles were present in a hydrated state. Although recent studies (*25*) suggest that real atmospheric aerosol particles likely remain hydrated even to low RH, the RH values in region III (44 to 52%) were near the efflorescence point of ammonium sulfate, below which laboratory data show a drop in $\gamma(N_2O_5)$ for pure $(NH_4)_2SO_4$ (*14*, *16*, *17*). Regardless of the precise mechanism, the important conclusion is that $\gamma(N_2O_5)$ is highly variable and appears to be a function of aerosol composition, particularly sulfate mass or sulfate-to-organic ratio.

This result has implications for the regional-scale NO_x burden and VOC oxidation, both of which affect the photochemical production of ozone. For example, a plume of NO_2 emitted at dusk into an air mass with loss rate coefficients for NO_3 and N_2O_5 characteristic of region I will undergo >90% irreversible loss of NO_x in a 10-hour night, whereas the same plume emitted into an air mass with NO_3 and N_2O_5 loss rate coefficients similar to those in region III will lose only 50% of its NO_x in the same time period. Nocturnal VOC processing will also be affected by the N_2O_5 loss rate because it influences the amount of NO_3, a potent oxidant. Mixing ratios of NO_3 in region I (Fig. 3D) were on the order of tens of parts per trillion by volume (pptv), whereas those in region III varied up to nearly 400 pptv, almost exclusively because of the difference in the loss rate for N_2O_5. The corresponding lifetime for many anthropogenic alkenes (other than ethene) with respect to NO_3 oxidation would change from about 50 to 5 hours (*26*). Such larger alkenes are among the most efficient for photochemical ozone production during the day (*27*). Therefore, the efficiency of N_2O_5 hydrolysis at night regulates both NO_x and reactive hydrocarbon abundances at sunrise, when photochemical ozone production begins.

That the variability in $\gamma(N_2O_5)$ appears to be most strongly correlated with the aerosol sulfate loading implies that there is a potential interaction between the emissions of SO_2, the NO_x budget, and regional O_3 formation. It is well understood that sulfate aerosol arising from anthropogenic SO_2 emissions provides a surface on which heterogeneous NO_x processing may occur. Less well understood, however, has been the magnitude of and variability in $\gamma(N_2O_5)$ and its dependence on aerosol sulfate. The only previous modeling study (*10*) to explicitly consider the interaction between SO_2 emission, sulfate aerosol, NO_x loss, and O_3 production assumed a constant, large value of $\gamma(N_2O_5) = 0.1$ on the basis of laboratory data available at that time (*28*). The study concluded that changes in SO_2 emissions would have a negligible effect on NO_x lifetimes and regional O_3 because the heterogeneous hydrolysis of N_2O_5 would be saturated (i.e., it would go fully to completion) for any reasonable aerosol surface area. The range of $\gamma(N_2O_5)$ determined here and the apparent variation of $\gamma(N_2O_5)$ with aerosol sulfate show that emission of SO_2, followed by its conversion to particulate sulfate, can indeed decrease the lifetime of NO_x and therefore influence photochemical ozone production. Further regional-scale model studies with realistic parameterizations of $\gamma(N_2O_5)$ are

required to quantify such an effect; if it were shown to be important, however, it could have implications for ozone mitigation strategies.

The variability of $\gamma(N_2O_5)$ with aerosol composition has potential impacts on other issues. They include the export of NO_x from the boundary layer to the free troposphere, the global burden of oxidants such as O_3 and OH (*10*), and the seasonal variations in NO_x and related chemistry. Our results point toward such influences, but additional in situ measurements of NO_x, NO_3, N_2O_5, O_3, VOC, and aerosol from aircraft and other platforms in different locations and seasons will be required to address these questions.

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Materials and Methods
SOM Text
Figs. S1 to S3
References

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An Unusual Marine Crocodyliform from the Jurassic-Cretaceous Boundary of Patagonia

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Remains of the marine crocodyliform *Dakosaurus andiniensis* from western South America reveal a lineage that drastically deviated from the skull morphology that characterizes marine crocodyliforms. The snout and lower jaw are extremely robust, short, and high and only bear a few large teeth with serrated edges (resembling those of some terrestrial carnivorous archosaurs). This unusual morphology contrasts with the long and gracile snout and lower jaws bearing numerous teeth, which are present in the closest relatives of *D. andiniensis* (and interpreted as indicating feeding on small fish or mollusks). Thus, the morphological diversity of pelagic marine crocodyliforms was wider than had been thought.

The fossil record of Crocodyliformes (crocodiles and extinct relatives) shows a wide morphological and ecological diversity. One of the most remarkable examples is Thalattosuchia, the only group of archosaurs completely adapted to the marine environment (*1*). This group is characterized by numerous features, including an extremely long and tubular hyperdentate snout (*1*, *2*). Here we describe a fossil crocodyliform from Patagonia that further expands this variation.

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In the Southern Hemisphere, most Mesozoic marine crocodyliforms have come from the Vaca Muerta Formation (*3*–*5*) in the Neuquén Basin (western Argentina; fig. S1). An extremely fragmentary crocodyliform specimen was previously discovered in this unit and named *Dakosaurus andiniensis* (*6*) because of some similarities with *D. maximus* (*7*) from the Jurassic in Europe. However, the fragmentary nature of this enigmatic material offered few answers about the habits and relationships of this large marine crocodyliform.

Two new specimens of *D. andiniensis* were recently found in Pampa Tril (fig. S1)—a rich, fossiliferous locality of the Vaca Muerta Formation—and are referred to this taxon because of the presence of autapomorphic characters for a marine crocodyliform (*8*). One of these includes a lower jaw (specimen identification: MOZ 6140P), and the other (MOZ 6146P) consists of an almost-complete skull and lower jaws (Fig. 1 and fig. S2). The new skull is almost complete and reveals an unusual skull and dental morphology. The skull and mandible are approximately 80 cm long from the anterior end to the cranio-mandibular articulation. The snout is high with respect to its anteroposterior length (Fig. 1 and fig. S2), compared with all other marine crocodyliforms (*2*–*9*), and measures 42 cm long and 15.3 cm high (measured at the anteroposterior midpoint of the rostrum). The lateromedial width of the rostrum is subequal to its dorsoventral depth. Anteriorly, the rostrum tapers rapidly, producing an unusual bullet-shaped skull. Most of the dorsal surface of the snout is convex and level with the dorsal surface of the frontal and supratemporal region. The subcircular orbit faces laterally and is large, constituting approximately 18% of the skull length. A large scleral ring is preserved in this opening. The elongated antorbital fossa is obliquely oriented, and the lacrimal, nasal, maxilla, and jugal bones form its margins, as in metriorhynchid thalattosuchians (*2*–*10*).

The premaxilla is only preserved on the left side and encloses a large narial opening, although the dorsomedial region of this element is unknown for this taxon. The maxilla is notably short and high and extends dorsally, contacting its counterpart and separating the nasals from the premaxilla. This element contributes to 65% of the rostral length. The nasals are short and broad, but they project posteroventrally as a long and acute process onto the lateral surface of the snout. The lacrimals are only exposed on the lateral surface of the rostrum and are dorsally sutured to the extensive prefrontal and nasals. The enlarged prefrontal extends onto the lateral surface of the snout and overhangs the orbit, a synapomorphic character of metriorhynchids (*2*).

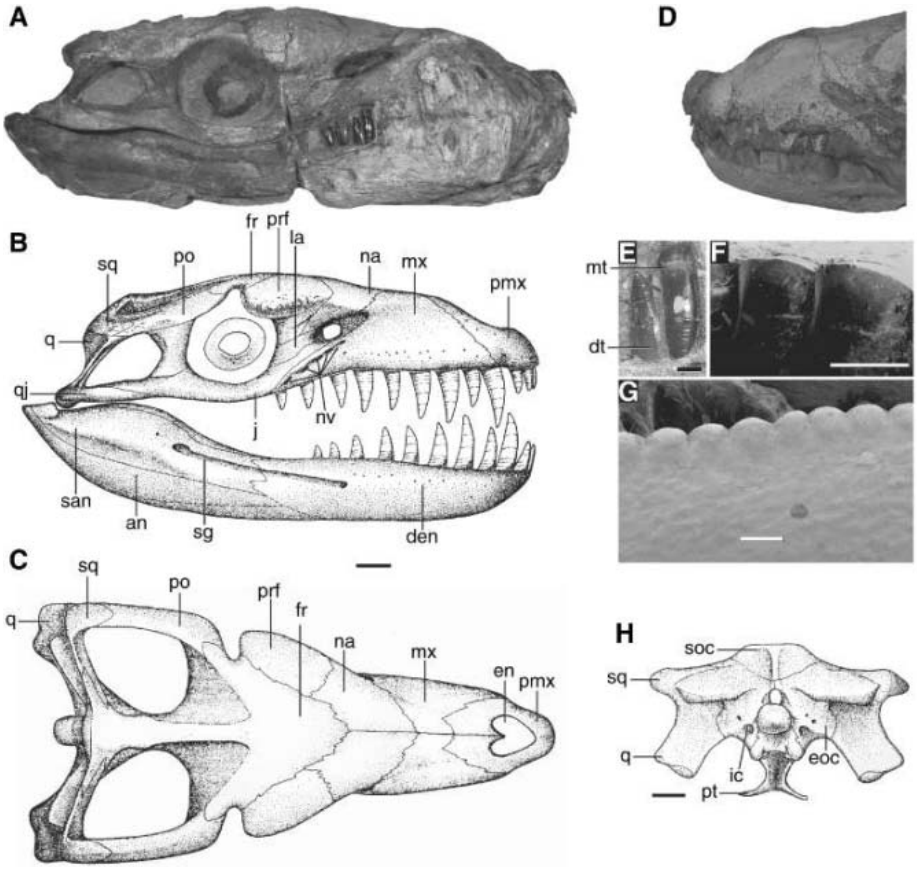

Fig. 1. *D. andiniensis* MOZ 6146P in (**A**) right lateral view. Skull reconstruction in lateral (**B**), dorsal (**C**), and occipital (**H**) views (based on left and right sides). (**D**) Rostrum in left dorsolateral view. (**E**) Posterior maxillary and dentary teeth. (**F** and **G**) Mesial denticles in mesial (F) and buccal (G) views. Scale bars, 5 cm [(A) to (D) and (H)]; 5 mm, (E); and 500 μm [(F) and (G)]. Abbreviations: an, angular; den, dentary; dt, dentary tooth; en, external nares; eoc, exoccipital; fr, frontal; ic, internal carotid foramen; la, lacrimal; mt, maxillary tooth; mx, maxilla; na, nasal; nv, neurovascular foramina; pmx, premaxilla; po, postorbital; prf, prefrontal; pt, pterygoid; q, quadrate; qj, quadratojugal; san, surangular; sg, surangular groove; soc, supraoccipital; sq, squamosal.

The frontals and parietals are completely fused into single elements, as in all mesoeucrocodylians (*10*). The straight frontal-nasal suture runs at a 45° angle with the sagittal plane, resembling the condition of *D. maximus* (*7*). The squamosal has a short anterior branch, and the postorbital extends ventrally on the lateral surface of the postorbital bar, continuous with the lateral surface of the jugal as in all thalattosuchians (*10*). The quadrate is well developed, with robust articular condyles, and it contacts the ventrolateral flange of the exoccipital as in all crocodyliforms (*10*). The basioccipital is low and bears small basioccipital tubera, contrasting with the developed condition of marine crocodyliforms. The exoccipital bears a large foramen for the internal carotid artery on its ventrolateral flange. The palatines form an extended secondary palate and enclose with pterygoids a wide choanal opening.

The mandible is high, robust, and slightly diverges posteriorly, following the narrow outline of the skull, which contrasts with the low and gracile morphology of other marine crocodyliforms (*1*, *2*, *11*). The mandibular symphysis is short, and its external surface is slightly convex and dorsoventrally high (MOZ 6140P; fig. S2). A broad and deep sulcus extends on the lateral surface of the dentaries and surangular, ending in a large foramen at both ends (as in *D. maximus*). The external mandibular fenestra is completely obliterated.

The upper dentition is composed of 3 premaxillary and 10 (or 11) large maxillary teeth, which is an unusually low number of teeth for a marine crocodyliform. Most thalattosuchians have between 25 and 40 small teeth, except for *D. maximus*, which has a minimum of 20 teeth in the upper tooth row (*2*). All preserved teeth of *D. andiniensis* are large, robust, poorly curved, and interlock extensively with the lower dentition (Fig. 1E). The crowns are lateromedially compressed and have serrated margins, resembling only those of *D. maximus* (*7*) among marine crocodyliforms. The denticles have a proportionately large basal length with respect to their height and are well separated from each other by broad cella and interdenticular slits (Fig. 1, F and G). The profile of the denticles is rounded in buccal view, but the serrations bear a sharp cutting edge on the mesial and distal margins (Fig. 1F). The outer enamel surface of all preserved teeth is divided into a basal smooth zone and a wrinkled apical region, with distinct, ring-like depressions.

This dental morphology is unique among marine reptiles; only some mosasaurs have serrated teeth, but they have remarkably small denticles (*12*). In contrast, the presence of denticles is common among terrestrial carnivorous archosaurs, including some crocodyliforms [e.g., *Baurusuchus*, *Iberosuchus*, *Sebecus*, and *Pristichampsus* (*1*, *9*, *13*, *14*)]. However, the serrated teeth of terrestrial crocodyliforms are chisel-shaped, with a shorter basal length, larger diaphyseal height, and narrow interdenticular slits (*12*, *14*–*16*). These differences are consistent with the independent origin of ziphodont dentition in *Dakosaurus* inferred from the phylogenetic results.

A phylogenetic data set was gathered considering representatives of all major clades of Crocodyliformes (*17*, *18*). The cladistic analysis places *D. andiniensis* as closely related to *D. maximus* (Fig. 2), as indicated by the presence of a proportionately higher rostrum and lateromedially compressed and serrated teeth. This group is deeply nested within Metriorhynchidae, the clade of crocodyliforms with the most remarkable adaptations to the marine environment [e.g., paddle-like forelimbs, hypocercal tail, osteoporotic-like bone (*19*), and hypertrophied nasal salt glands (*20*)]. This group is well supported by the data and diagnosed by numerous cranial synapomorphies present in *D. andiniensis* (*17*). The available postcranial material of *D. andiniensis* is too scarce to assess if the swimming capabilities of this crocodyliform were similar to those of other metriorhynchids.

The phylogenetic hypothesis implies that the *Dakosaurus* lineage evolved from the ancestral gracile condition present in most thalattosuchians (Fig. 2). Within this framework, the European *D. maximus* represents an initial stage in the evolution of a lineage that departs from the above-mentioned conditions, showing the acquisition of relatively enlarged teeth with serrated margins and a moderately high snout, but preserving many plesiomorphies of other metriorhynchids (e.g., large number of teeth, elongated symphysis, and snout length occupying more than 60% of the skull). However, the unusual morphology of *D. andiniensis* creates a large morphological gap between this taxon and all other marine crocodyliforms.

One of the most striking differences is the extremely high and robust rostrum in *D. andiniensis*. We considered the variation in rostral height and length through the optimization of their ratio across the phylogenetic tree of Crocodyliformes using the maximum parsimony criterion (Fig. 3). As optimized in the tree, this analysis illustrates the differences between

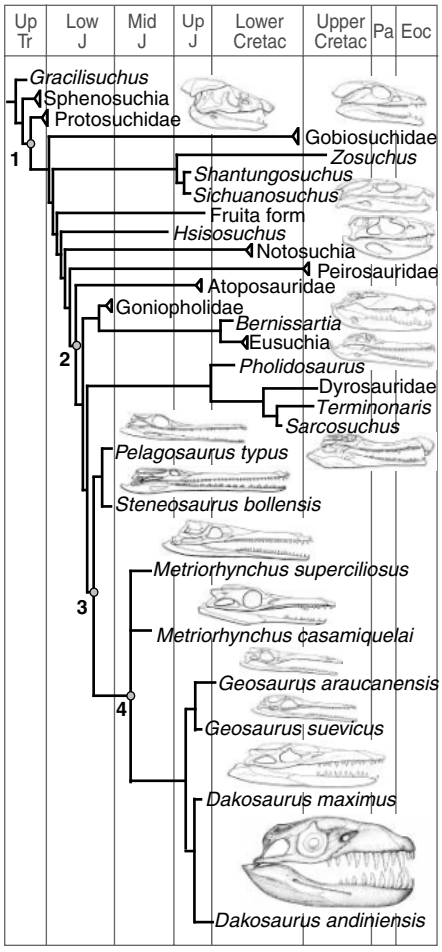

Fig. 2. Phylogenetic relationships of Crocodyliformes obtained in the cladistic analysis, plotted against geochronologic epochs (strict consensus of most parsimonious trees; some taxa distantly related to *D. andiniensis* collapsed into triangular clades). Only skull figures of Thalattosuchia were drawn to the same scale (*17*). Numbered nodes: 1, Crocodyliformes; 2, Neosuchia; 3, Thalattosuchia; and 4, Metriorhynchidae. Further phylogenetic information is available in (*17*).

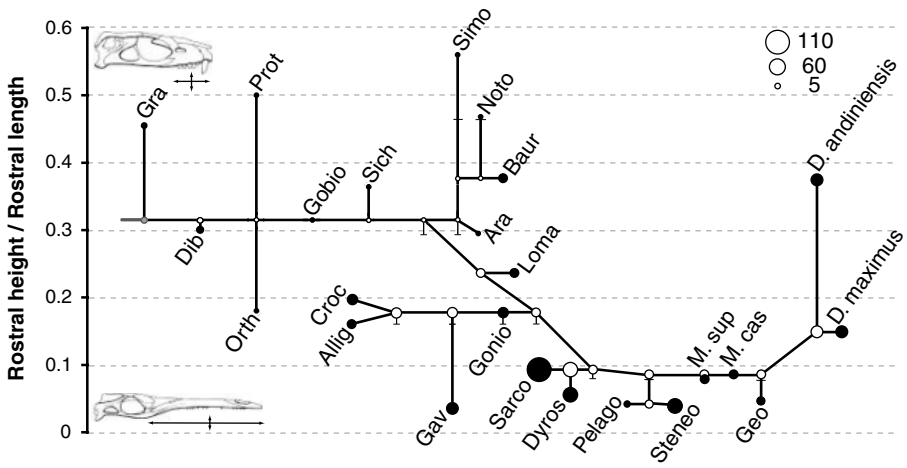

Fig. 3. Phylogenetic tree of Crocodyliformes displaying the evolution of rostral shape, as measured by the rostral height/rostral length ratio optimized using TNT (*28*, *29*). The root of the tree located on the left side of the figure (marked in gray) and derived forms are toward the right. The vertical location of the nodes is determined by the ratio values following the ordinate axis [solid circles, measured species (*17*); empty circles, inferred ancestral values; error bars, ranges of possible ancestral values]. Circle size represents the absolute value of rostral length measured in terminal taxa and inferred for ancestral nodes (scale for circle size and rostral length in cm in top right corner) (*17*). Abbreviations: Gra, *Gracilisuchus*; Dib, *Dibothrosuchus*; Orth, *Orthosuchus*; Prot, *Protosuchus*; Gobio, *Gobiosuchus*; Sich, *Sichuanosuchus*; Simo, *Simosuchus*; Noto, *Notosuchus*; Baur, *Baurusuchus*; Ara, *Araripesuchus*; Loma, *Lomasuchus*; Gonio, *Goniopholis*; Gav, *Gavialis*; Croc, *Crocodylus niloticus*; Allig, *Alligator*; Sarco, *Sarcosuchus*; Dyros, *Dyrosaurus*; Steneo, *Steneosaurus*; Pelago, *Pelagosaurus*; M. sup, *Metriorhynchus superciliosus*; M. cas, *Metriorhynchus casamiquelai*; Geo, *Geosaurus araucanensis*.

D. andiniensis and other marine taxa and reveals the major trends in rostral change along the evolutionary history of Crocodyliformes.

The large diversity of rostral shapes among basal terrestrial crocodyliforms (*21*) is reflected in the disparity of rostral height/length ratios among these small forms (Fig. 3, left). However, this graph shows a clear phylogenetic trend in neosuchian crocodyliforms toward longer rostra that are proportionately low dorsoventrally (Fig. 3, right). These morphological changes coincide with a shift toward the aquatic habits inferred for most neosuchian taxa and have been explained as adaptations to this environment, related changes in feeding strategies, and increases in mechanical resistance in their rostra (*1*, *9*, *22*).

Although different rostral morphologies are present in living crocodylians (*23*) and moderate cases of rostral shortening have been reported in some longirostrine groups (*17*, *24*, *25*), the general trend toward long and low snouts is present in most neosuchian groups (Fig. 3). This trend reaches an extreme condition in thalattosuchian crocodyliforms, depicting the characteristic elongated and gracile snouts of these marine crocodyliforms. The hyperdentate tubular rostrum in this group has long been considered as an adaptation to feeding on small agile prey, such as mollusks (*26*) or fishes [based on the diet of extant crocodylians with similar rostral morphology (e.g., *Gavialis*) (*1*, *9*, *22*)]. The feeding strategy of these taxa is usually inferred to be based on rapid lateral movements, facilitated by the large angular speed and low hydrodynamic resistance of their elongated and low rostra (*1*, *9*, *22*).

The *Dakosaurus* lineage appears to have reversed this trend in a drastic morphological change, with *D. maximus* an incipient representative of this condition and *D. andiniensis* the most extreme case of rostral modification (Fig. 3). The relatively short and high rostrum and ziphodont dentition probably reflects a modified feeding strategy, because the hydrodynamic advantages allowing rapid lateral movements would not be present in *D. andiniensis*. Although the snout height/length ratios depict similar values for *D. andiniensis* and some terrestrial crocodyliforms (e.g., *Baurusuchus*), there are remarkable differences in other aspects of their rostral shape, such as the reduced width of the snout and the vertically orientated maxillae of these terrestrial forms.

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The Late Miocene Radiation of Modern Felidae: A Genetic Assessment

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Modern felid species descend from relatively recent (<11 million years ago) divergence and speciation events that produced successful predatory carnivores worldwide but that have confounded taxonomic classifications. A highly resolved molecular phylogeny with divergence dates for all living cat species, derived from autosomal, X-linked, Y-linked, and mitochondrial gene segments (22,789 base pairs) and 16 fossil calibrations define eight principal lineages produced through at least 10 intercontinental migrations facilitated by sea-level fluctuations. A ghost lineage analysis indicates that available felid fossils underestimate (i.e., unrepresented basal branch length) first occurrence by an average of 76%, revealing a low representation of felid lineages in paleontological remains. The phylogenetic performance of distinct gene classes showed that Y-chromosome segments are appreciably more informative than mitochondrial DNA, X-linked, or autosomal genes in resolving the rapid Felidae species radiation.

The first felidlike carnivores appeared in the Oligocene, approximately 35 million years ago (Ma). Living cat species (subfamily Felinae) originated in the late Miocene and evolved into one of the world's most successful carnivore families, inhabiting all the continents except Antarctica (*1*, *2*). Understanding their evolutionary history and establishing a consensus taxonomic nomenclature has been complicated by rapid and very recent speciation events, few distinguishing dental and skeletal characteristics, incidents of parallel evolution, and an incomplete fossil record (*1*–*5*). Recent analyses (*6*–*8*) identified eight major felid lineages, although their chronology, branching order, and exact composition remained unresolved (*4*–*8*). Here, we present an analysis of DNA sequence from 19 independent autosomal (aDNA), five X-linked (xDNA), six Y-linked (yDNA), and nine mitochondrial (mtDNA) gene segments (tables S1 to S3) sampled across the 37 living felid species plus 7 outgroup species representing each feliform carnivoran family (*9*).

We present a phylogenetic analysis (Fig. 1) for nuclear genes (nDNA) [combined y, x, and aDNA = 18,853 base pairs (bp)] that leads to several conclusions. First, the eight Felidae lineages are strongly supported by bootstrap analyses and Bayesian posterior probabilities (BPP) for the nDNA data and most of the other separate gene partitions (Table 1 and figs. S1 to S11), by rare shared derived indels, including endogenous retroviral families in the domestic cat lineage (*10*), by transposed nuclear mtDNA sequences (*Numt*) in the domestic cat (node 9) and *Panthera* lineages (node 33) (*11*, *12*) (Table 1 and table S7), by 11 to 65 diagnostic sites for individual lineages (tables S5 and S8), and by amino acid data analyses of 14 genes (1457 sites) (tables S9 and S10 and fig. S1). Second, the four species previously unassigned to any lineage (marbled cat, serval, pallas cat, and rusty spotted cat) (*6*) have now been confidently placed. Third, the hierarchy and timing of divergences among the eight lineages are clarified (Fig. 1 and Table 1). Fourth, the phylogenetic relationships among the nonfelid species of hyenas, mongoose, civets, and linsang corroborate previous inferences with strong support (*13*, *14*).

The radiation of modern felids began with the divergence of the *Panthera* lineage leading to the clouded leopard and the "great roaring cats" of the *Panthera* genus (node 33 in Fig. 1). Support for this basal position was strong (88 to 100%) with all analytic methods and gene partitions (Table 1 and table S4) contrasting with some previous results that suggested a more internal position for the big cats (*7*). The split of the *Panthera* lineage was followed by a rapid progression of divergence events. The first led to the bay cat lineage, a modern assemblage of three Asian species (bay cat, marbled cat, and Asian golden cat) (node 31), followed by divergences of the caracal lineage, with three modern African species (caracal, serval, and African golden cat) (node 29) and of the ocelot lineage (node 23), consisting of seven Neotropical species. Bootstrap support (BS) for the nodes that produced these three early divergences (nodes 2 to 4) was moderate (74 to 97% nDNA BS) relative to nodes defining lineage groups (23, 29, and 31) with 100% nDNA BS. A more recent clade, including four lineages (lynx, puma, leopard cat, and domestic cat lineages) (node 5), is well supported (97 to 99% nDNA BS). The divergence of the lynx lineage was followed very closely by the appearance of the puma lineage (Fig. 1). However, these two North American groups were united as sister groups in some analyses using different data partitions and phylogenetic algorithms (figs. S6 to S11 and

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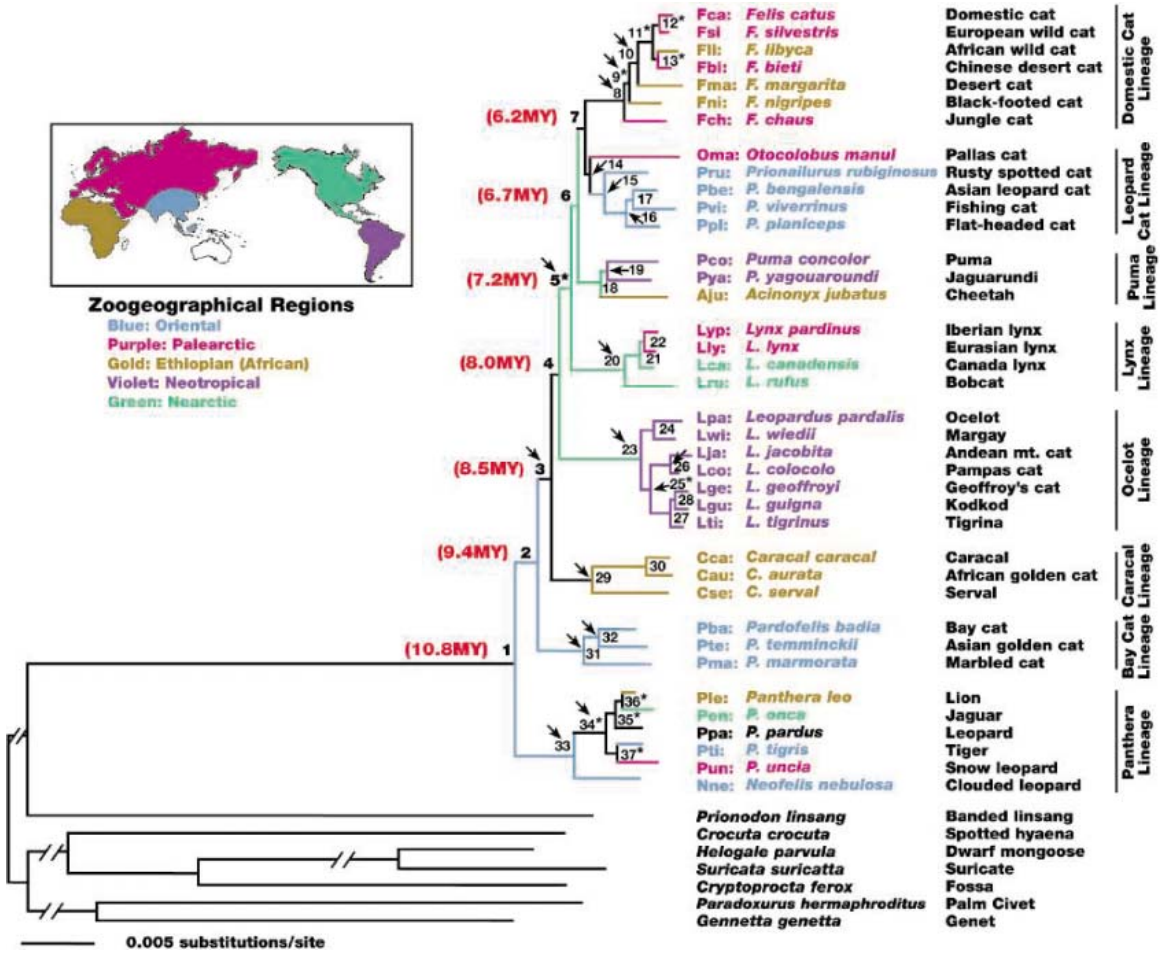

Fig. 1. Phylogenetic relations among felid species and outgroup taxa depicted in a maximum likelihood tree [tree bisection-reconnection (TBR) search and general time reversible (GTR) + G + I model of sequence evolution from 18,853 bp of nDNA concatenated data] (*9*). Terminal nodes are labeled with three-letter codes, scientific name, and common name, and felid species are grouped into eight major lineages. Scientific names and branches are color coded to depict recent and historic zoogeographical regions (Oriental, Palearctic, Ethiopian, Neotropical, and Nearctic), as inferred from current distributions, fossil records, and our phylogenetic analyses (*1–5, 9*). Branches in black reflect either less certain historical interpretations or geographic distributions beyond one zoogeographic zone. Nodes 1 to 37 are numbered, and an asterisk indicates relatively low resolution (Table 1). Estimated divergence dates of lineage-defining nodes (*1–7*) are in red. Rare insertion/deletions supporting lineages as shared derived cladistic characters are indicated by an arrow (Table 1).

table S5). The two most recently derived groups were the domestic cat and leopard cat lineages (99 to 100% nDNA BS) (node 7). Support for inclusion of the pallas cat within the leopard cat lineage was moderate (76 to 100% nDNA BS) but included a single insertion/deletion (APP + 1) (Table 1 and table S7).

Together, each of the eight lineages received strong BS and BPP of 100% using nDNA, with slightly less support for the hierarchical intralineage relationships (Table 1). A few internal nodes with lower support must remain as uncertain (asterisk in Fig. 1), including the position of Andean mountain cat within the ocelot lineage, the branching order of jungle cat and black-footed cat within the domestic cat lineage, and the precise hierarchy among *Panthera* species. Support for these relations was low, probably as a result of inconsistent sorting patterns of ancestral polymorphisms. Even so, the overall support of the major nodes is strong, increasing confidence in the proposed topology (Fig. 1).

The earliest records of the Felinae are ascribed to late Miocene (~9 Ma) *Felis attica* fossils from western Eurasia (*15*). Estimates of divergence dates using a Bayesian approach with 16 fossil calibration dates (*9*) indicate that the major felid lineages were established during a short evolutionary time period (10.8 to 6.2 Ma) (Fig. 1 and Table 1). Within-lineage divergences occurred during the late Miocene and early Pliocene (6.4 to 2.9 Ma), when sea levels were generally 90 to 100 m above modern levels (*16*). A second major surge in species differentiation followed from 3.1 to 0.7 Ma, with the initial appearance of 27 of 37 extant species that comprise modern felids (Fig. 1 and Table 1). These late Pliocene-Pleistocene species divergence episodes occurred during a period of relatively low sea levels before the onset of Pleistocene glacial oscillations (Fig. 2).

We propose a plausible biogeographic hypothesis of felid evolutionary history (Fig. 2) based on our results and geological events (*16–19*). The most parsimonious scenario implies that modern felids arose in Asia with the divergence of the *Panthera* lineage 10.8 Ma and, subsequently, the bay cat lineage 9.4 Ma. These dates correspond to extremely low sea levels of the late Miocene (Fig. 2). An early migration (M1) occurred 8.5 to 5.6 Ma when a progenitor of the caracal lineage arrived in Africa. The second migration (M2) relocated a common ancestor to five felid lineages (ocelot, lynx, puma, leopard cat, and domestic cat) across the Bering land bridge to North America for the first time, 8.5 to 8.0 Ma (Fig. 2). This New World migration (M2) would be coincident with a period when a rich assemblage of Eurasian carnivores (ursid, procyonid, mustelid, and saber-toothed felid species) is postulated to have crossed from Eurasia to North America (*19*) and would precede the differentiation of the ocelot, puma, and lynx lineages 8.0 to 6.7 Ma (Fig. 1). The divergence of the ocelot lineage occurred 8.0 to 2.9 Ma (Table 1, nodes 4 and 23), and further species differentiation was likely facilitated by the Panamanian land bridge 2.7 Ma (M3) and faunal exchange with South America (*20*). Between 6.7 and 6.2 Ma the domestic cat and leopard cat lineages probably diverged from Eurasian forebears that either had remained in Asia (split off from the New World M2 immigrants) or derived from American migrants that crossed the Bering land bridge (M4), as has been postulated for several Canidae and Camelidae species (*21*).

Today, four major Felidae lineages occur within zoogeographical regions of their orig-

Table 1. Summary of support values for each of the nodes depicted in Fig. 1, including Bayesian estimated date of divergence, with the corresponding 95% credibility interval, the estimated time before the node, and bootstrap support values for the minimum evolution (ME), maximum parsimony (MP), and maximum likelihood (ML) analyses and Bayesian (BAY) posterior probabilities (*9*). Bootstrap values <50% are marked (<). Indels that support each node are noted by the gene abbreviation where they occur, the number of base pairs inserted (+) or deleted (–), and an asterisk denoting a possible short tandem repeat element (STR) (table S7). RD114 and FeLV are endogenous retroviral families (*10*), and *Numt* are large nuclear insertions of mtDNA (*11*, *12*). Y-linked genes are in bold capital letters. Species abbreviations are defined in Fig. 1.

		Divergence Time (Ma)					Percentage Statistical Support											
Node	Description of node	Date (Ma)	Confidence interval	Time prior to node (My)	Divtime fossil Constraint (My)	Insertion/deletion variants[2]	nDNA ME	nDNA MP	nDNA ML	nDNA BAY	mt DNA ME	mt DNA MP	mt DNA ML	mt DNA BAY	Total DNA ME	Total DNA MP	Total DNA ML	Total DNA BAY
1	**Felidae base**	10.78	8.38, 14.45		<16.0		100	100	100	100	100	100	88	100	100	100	100	100
2	Bay cat lineage and node 3	9.43	7.36, 12.77	1.35			82	74	93	100	64	<	70	<	99	100	100	100
3	Caracal lineage and node 4	8.51	6.66, 11.56	0.92		**UBE1Y(+2)**	85	97	87	100	<	<	<	<	74	50	55	100
4	Ocelot lineage and node 5	8.05	6.30, 10.95	0.46	>5.0		90	79	80	100	<	<	<	<	70	40	55	100
5	Lynx lineage and node 6	7.15	5.62, 9.81	0.90	>5.3	**SRY5(-5)***	98	97	99	100	<	<	<	<	92	72	94	100
6	Puma lineage and node 7	6.70	5.27, 9.20	0.45			<	56	59	99	<	<	<	<	<	<	55	<
7	nodes 8 and 14	6.18	4.80, 8.55	0.52	>4.2		100	99	99	100	<	69	<	100	100	96	100	100
8	**Domestic cat lineage**	3.36	2.41, 4.88	2.82		**SMCY(+SINE), UBE1Y(+2)***, RD114, FeLV	100	100	100	100	100	100	100	100	100	100	100	100
9	(Fni, Fma, Fca, Fsi, Fli, Fbi)	3.04	2.16, 4.44	0.32		**SRY5(-9)**, *Numt* insert1	<	76	75	65	<	<	<	<	<	<	<	100
10	(Fma, Fca, Fsi, Fli, Fbi)	2.49	1.72, 3.67	0.55	>1.0		99	98	99	100	100	100	100	100	100	100	100	65
11	(Fca, Fsi, Fli, Fbi)	1.40	0.89, 2.16	1.09			100	100	100	100	<	100	89	100	100	100	100	100
12	(Fca, Fsi)	0.99	0.59, 1.62	0.41			62	<	54	63	<	<	<	<	<	<	<	<
13	(Fli, Fbi)	1.17	0.72, 1.86	0.23			76	68	68	100	<	<	<	<	<	<	<	<
14	**Leopard cat lineage**	5.86	4.53, 8.16	0.32	>1.0	APP(+1)	93	76	83	100	<	<	<	<	<	<	<	83
15	(Pru, Pbe, Pvi, Ppl)	4.59	3.42, 6.54	1.27		CLU(+2)	99	100	100	100	69	100	100	100	100	100	100	100
16	(Pbe, Pvi, Ppl)	2.94	2.04, 4.31	1.65		CLU(-1)	100	100	100	100	99	98	99	100	100	100	100	100
17	(Pvi, Ppl)	2.55	1.74, 3.82	0.39			81	72	72	100	100	100	100	100	100	100	100	100
18	**Puma lineage**	4.92	3.86, 6.92	1.78	>3.8		100	100	100	100	73	<	55	100	100	100	100	100
19	(Pco, Pya)	4.17	3.16, 6.01	0.75	>1.8	DGKG(-4)*, CLU(-1)*	99	100	100	100	<	<	<	56	78	94	100	100
20	**Lynx lineage**	3.24	2.53, 4.74	3.93	>2.5	CLU(-1), GNB(-1), ALAS(-2)*, **ZFY(-6)**	100	100	100	100	98	99	99	100	100	100	100	100
21	(Lca, Lyp, Lly)	1.61	1.06, 2.60	1.63			100	100	100	100	100	100	100	100	100	100	100	100
22	(Lyp, Lly)	1.18	0.70, 1.98	0.43			<	92	84	100	54	<	<	<	<	<	56	100
23	**Ocelot lineage[1]**	2.91	2.02, 4.25	5.15	<5.0	CLU(-1), DGKG(-3), GNB(-1), TCP (-1), TCP(+6)	100	100	100	100	100	100	99	100	100	100	100	100
24	(Lpa, Lwi)	1.58	1.01, 2.41	1.43			84	68	99	100	100	100	<	100	<	<	54	100
25	(Lja, Lco, Lti, Lge, Lgu)	2.43	1.68, 3.56	0.48	>1.0		100	99	<	100	98	52	100	100	100	100	100	100
26	(Lja, Lco)	1.80	1.18, 2.70	0.14			98	80	<	100	63	<	<	100	<	<	<	100
27	(Lti, Lge, Lgu)	0.93	0.56, 1.48	1.01			<	100	100	100	<	<	<	<	97	80	99	100
28	(Lge, Lgu)	0.74	0.41, 1.21	0.19		GNB(-3)*	75	96	90	100	100	100	100	100	100	100	100	100
29	**Caracal lineage**	5.59	4.14, 7.91	2.93	>3.8	CLU(+1), CLU(+1), **SMCY(-4)**	100	100	100	100	80	86	77	100	100	100	100	100
30	(Cca, Cau)	1.88	1.19, 2.93	3.71		GNB(-3), RASA(-3)*, **UBE1Y(-4)**	100	100	100	100	100	100	100	100	100	100	100	100
31	**Bay cat lineage**	5.86	4.27, 8.42	3.57		**PLP(+1), UBE1Y(-18)**	100	100	100	100	<	<	<	<	100	100	100	100
32	(Pba, Pte)	4.30	2.96, 6.42	1.56			<	100	100	100	100	100	100	100	100	100	100	100
33	**Panthera lineage**	6.37	4.47, 9.32	4.41	>3.8	**SRY3(+4)**, *Numt* insert 2	100	100	100	100	58	100	100	100	100	100	100	100
34	(Ple, Pon, Ppa, Pti, Pun)	3.72	2.44, 5.79	2.65		**SRY3(-7)**	100	100	100	100	64	100	100	100	100	100	100	100
35	(Ple, Pon, Ppa)	2.87	1.81, 4.63	0.85			90	88	93	100	<	<	<	<	<	<	68	100
36	(Ple, Pon)	2.06	1.22, 3.46	0.81			68	77	78	100	<	<	<	99	<	<	<	100
37	(Pti, Pun)	2.88	1.82, 4.62	0.84	>1.0		99	92	92	100	<	<	76	<	100	99	100	100

[1]The NNI ML search placed Lja basal to the six other species in the lineage, but with a lower score (-ln 66463.95 versus 66459.92), as did the ME and MP analyses. [2]Indel variants are indicated in combined alignment of all gene segments in figure S2.

inal establishment: the bay cat and leopard cat lineages (Oriental), the caracal lineage (Ethiopian), and the ocelot lineage (Neotropical) (Figs. 1 and 2). The other lineages include species inhabiting different continents, supporting the premise of six additional Pliocene/Pleistocene migrations (M5 to M10). Among them was the cheetah, which originated in the North American puma lineage (Fig. 1) and migrated to central Asia and Africa (M5). Similarly, progenitors of the Eurasian and Iberian lynxes migrated across the Bering peninsula to Eurasia 1.6 to 1.2 Ma (M6). Further, Asian-derived *Panthera* species spread into America (jaguar-M7 and lion-M8) and into Africa (lion and leopard-M9) (*22*). Our proposed scenario would also require Pleistocene migrations into Africa of the sand cat, black-footed cat, and African wild cat (M10). More temperate climates and substantially lower sea levels associated with major Pleistocene glaciations facilitated several other faunal movements between North America and Asia during this period, including pulses of dispersal by microtine rodents (*21*) and humans (*23*). Modern felids examined to date have relatively recent coalescent dates (*24*).

Although we employ 16 fossil dates (*9*), estimated molecular dates (Table 1) reveal large portions of felid history for which the fossil record is incomplete. By identifying the oldest fossil for every branch on the tree and comparing it with the Bayesian estimated molecular divergence date for that branch (table S6 and fig. S12), we estimated the average unrepresented basal branch length (UBBL) (*25*). This analysis indicated that the fossil record underestimates the first age of evolutionary divergences along each evolutionary branch on average by 76% or by 73% for the terminal branches and 79% for the internal branches. These figures are comparable to those derived for bats (Chiroptera) (*25*) and support the perception that a large portion of felid evolutionary history is not represented in the fossil record.

Our combined data set resulted in a fairly well resolved phylogenetic tree, but as in Rokas *et al*. (*26*), specific subsets of the data seldom produced comparable resolution or statistical support (figs. S1 to S11 and table S4). Of the four main genetic data groups, mtDNA was the most divergent, followed by yDNA. There were 1175 mtDNA parsimony informative sites (PI) among felids and 838 nDNA PI (443 aDNA, 279 yDNA, and 116 xDNA PI) (table S1). Despite the comparatively larger amount of data (and signal) (table S5), overall mtDNA variation was least robust in node resolution with a high mtDNA homoplasy index (HI) (0.705), compared with aDNA (0.197), xDNA (0.111), and yDNA (0.114). The 4456 bp of yDNA and the 11,166 bp of aDNA did the best at distinguishing the eight major lineages (eight of eight with >97% ML BS), whereas mtDNA genes (3936 bp) provided >80% ML BS for only four of these eight lineages. The yDNA genes also provided the most shared derived sites defining each lineage and the relative order of lineages (four of seven nodes with >83% ML BS) (*9*).

The evolutionary time frame and phylogenetic challenges for the Felidae are analogous to those encountered in great ape studies [e.g., (*27*, *28*)], in which, for example, only 60% of the phylogenetically informative sites or loci supported a generally accepted human/chimpanzee clade, whereas the remaining 40% supported alternative arrangements (*29*). Within the felid phylogeny, 21 of the 36 divergences occurred in less than 1.0 million years, and the seven basal nodes are spaced an average 600,000 years apart. Similar radiations are common throughout mammalian evolutionary history, which suggests that confident resolution of these will also require large, multigenic data sets.

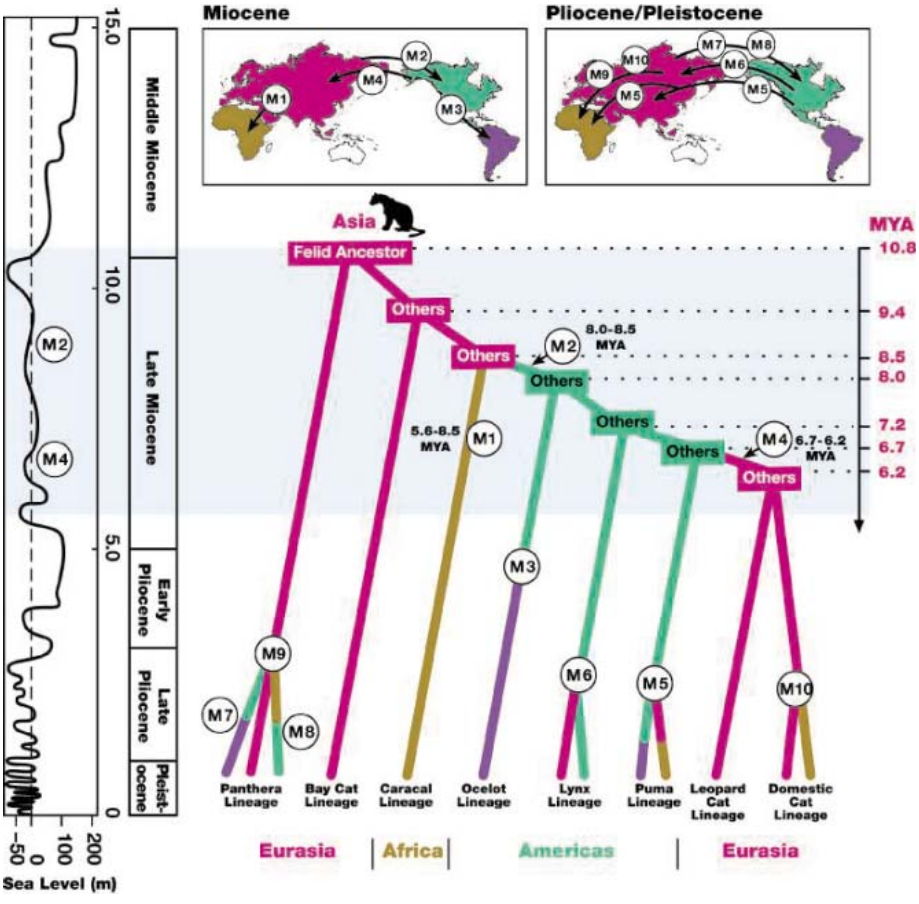

Fig. 2. A depiction of hierarchical divergence, estimated dates, and inferred intercontinental migrations along the phylogenetic lineages in Fig. 1 imputed from Bayesian dating, phylogenetic analyses, the fossil record, current species distributions, and an analysis of possible migration scenarios (*9*). Deduced intercontinental migrations (M1 to M10) and correspondence with major changes in worldwide sea levels, as depicted on a eustatic sea-level curve (on left) [modified from (*16*)], are described in the text.

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Materials and Methods
Figs. S1 to S12
Tables S1 to S10
References

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Alterations in 5-HT$_{1B}$ Receptor Function by p11 in Depression-Like States

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The pathophysiology of depression remains enigmatic, although abnormalities in serotonin signaling have been implicated. We have found that the serotonin 1B receptor [5-hydroxytryptamine (5-HT$_{1B}$) receptor] interacts with p11. p11 increases localization of 5-HT$_{1B}$ receptors at the cell surface. p11 is increased in rodent brains by antidepressants or electroconvulsive therapy, but decreased in an animal model of depression and in brain tissue from depressed patients. Overexpression of p11 increases 5-HT$_{1B}$ receptor function in cells and recapitulates certain behaviors seen after antidepressant treatment in mice. p11 knockout mice exhibit a depression-like phenotype and have reduced responsiveness to 5-HT$_{1B}$ receptor agonists and reduced behavioral reactions to an antidepressant.

The serotonin system plays a key modulatory role in a plethora of functions of the central nervous system in physiological and disease states (*1*, *2*). Compounds that alter either the reuptake or the metabolism of serotonin are used as medications against many neuropsychiatric disorders (*1*–*4*). A better understanding of the role of individual serotonin receptors in mediating the effects of these medications would improve our comprehension of the etiology of certain neuropsychiatric disease states and enhance our ability to design more effective medications. There are 14 different serotonin receptors (*2*), some of which have multiple splice variants that enable binding of distinct sets of intracellular proteins (*5*). 5-HT$_{1B}$ receptors play a crucial role in regulating serotonin neurotransmission, as they serve as both autoreceptors on serotonin-containing neurons originating from the raphe nuclei and heteroreceptors on several neurons that do not

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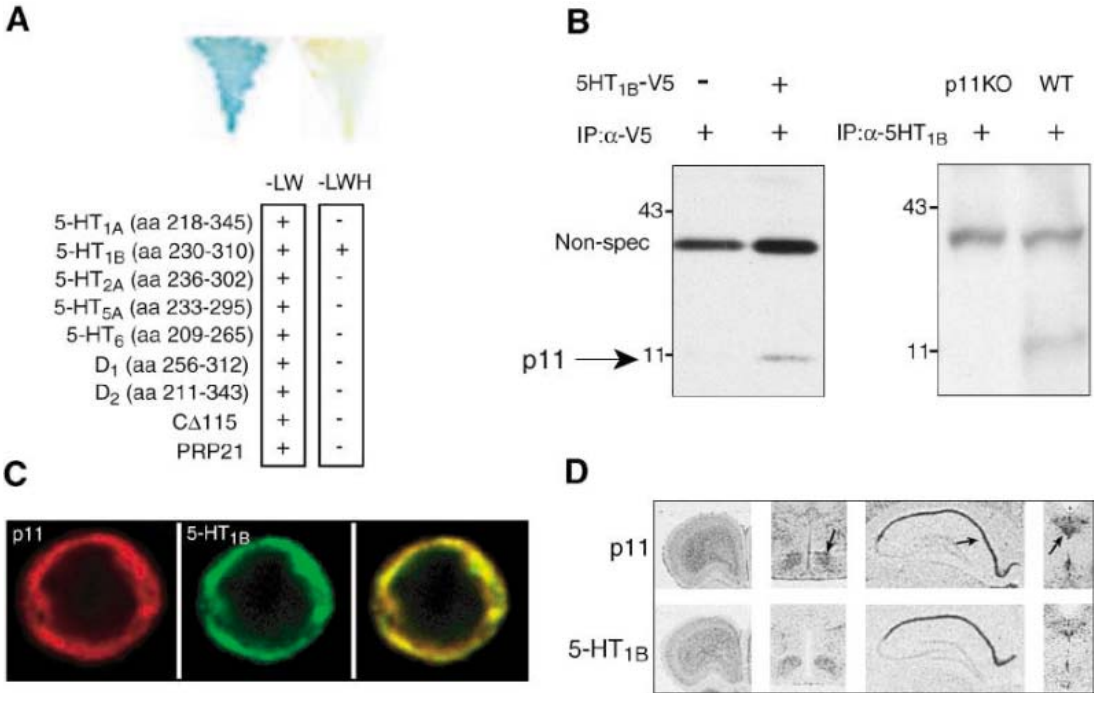

Fig. 1. Identification of an interaction between 5-HT$_{1B}$ receptors and p11. (**A**) Results from a yeast two-hybrid screen showing an interaction of p11 with the 5-HT$_{1B}$ receptor (left; blue color), but not with an unrelated bait (CΔ115; right; no color), or with pRP21, 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_{5A}$, 5-HT$_{6}$, D$_{1}$, or D$_{2}$ receptors. (**B**) Coimmunoprecipitation confirming that p11 interacts with (left panel) V5 epitope–tagged 5-HT$_{1B}$ receptors in HeLa cells and with (right panel) native 5-HT$_{1B}$ receptors in brain tissue from wild-type, but not p11 KO, mice. The immunoprecipitates were analyzed by Western blotting using a p11-specific antibody. The nonspecific band corresponds to the light chains of the antibodies against V5 or 5-HT$_{1B}$ receptors (α-V5 and α-5HT$_{1B}$). (**C**) Immunofluorescence staining of p11 (left, red fluorescence), V5 epitope–tagged 5-HT$_{1B}$ receptors (middle, green fluorescence) and their colocalization (right, yellow fluorescence) at the cell surface in HeLa cells. (**D**) In situ hybridization made on coronal sections from a rat brain showing that the distribution of p11 mRNA is similar to that of 5-HT$_{1B}$ receptor mRNA in (left to right) frontal cortex, ventromedial hypothalamus (arrow), hippocampus (arrow), and raphe nuclei (arrow).

contain serotonin (*6*, *7*). Pharmacologic and genetic studies have suggested a role for 5-HT_{1B} receptors in the pathophysiology of obsessive compulsive disorder, drug addiction, depression, anxiety, aggression, and sleep (*1*, *7*, *8*).

To better understand the function of 5-HT_{1B} receptors, we used the third intracellular loop of this receptor as bait in a yeast two-hybrid

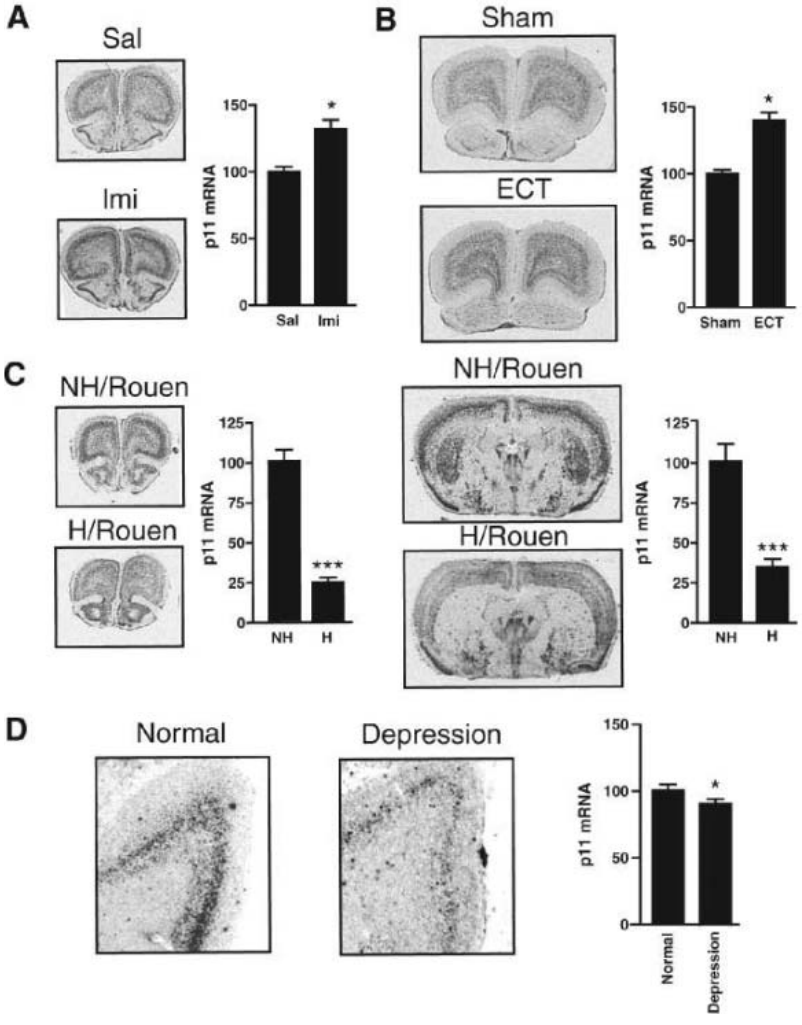

Fig. 2. Regulation of p11 expression by antidepressant treatments and in depression-like states. In situ hybridization illustrating an up-regulation of p11 mRNA in the forebrain following (**A**) repeated treatment with imipramine [10 mg/kg per day, intraperitoneally (i.p.) for 14 days] in mice ($n = 8$ per group) and (**B**) electroconvulsive therapy (ECT) for 10 days in rats ($n = 5$ per group). Conversely, p11 mRNA was down-regulated in (**C**) the forebrain in helpless H/Rouen versus nonhelpless NH/Rouen mice ($n = 10$ per group) and (**D**) in patients who suffered from unipolar major depression ($n = 15$ per group). Data from the anterior (A; B; C, left; D) and posterior (C, right) cingulate cortices were normalized to the corresponding controls and represent means ± SEM. $*P < 0.05$, $***P < 0.001$ versus control by Student's *t* test.

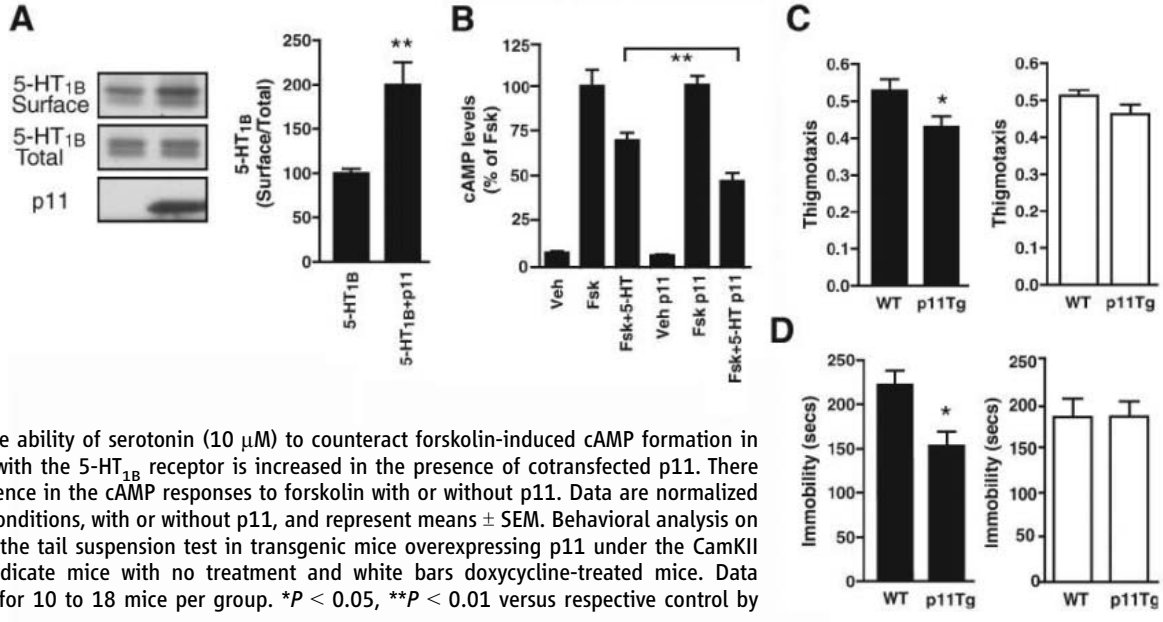

Fig. 3. Biochemical and behavioral effects of overexpression of p11 in cells and in transgenic mice. (**A**) Biotinylation experiment from COS-7 cells showing that p11 increases the amount of 5-HT_{1B} receptors at the cell surface. Data were normalized to the amount in cells transfected only with 5-HT_{1B} receptors and represent means ± SEM for three experiments, each in triplicate. (**B**) The ability of serotonin (10 μM) to counteract forskolin-induced cAMP formation in COS-7 cells transfected with the 5-HT_{1B} receptor is increased in the presence of cotransfected p11. There was no significant difference in the cAMP responses to forskolin with or without p11. Data are normalized to forskolin-stimulated conditions, with or without p11, and represent means ± SEM. Behavioral analysis on (**C**) thigmotaxis and (**D**) the tail suspension test in transgenic mice overexpressing p11 under the CamKII promoter. Black bars indicate mice with no treatment and white bars doxycycline-treated mice. Data represent means ± SEM for 10 to 18 mice per group. $*P < 0.05$, $**P < 0.01$ versus respective control by Student's *t* test.

screen (*9*). Twenty-six out of 29 double-positive prey clones encoded the gene for p11 (also called S100A10, 42C, calpactin I light chain, and annexin II light chain), a member of the S100 EF-hand protein family (*10*). p11 interacted with 5-HT_{1B} receptors, but not with 5-HT_{1A}, 5-HT_{2A}, 5-HT_{5A}, 5-HT_6, dopamine D_1 or D_2 receptors, two irrelevant baits (CΔ115 and pRP21), or the empty plasmid, which showed the specificity of this interaction (Fig. 1A). p11 was found to coimmunoprecipitate with 5-HT_{1B} receptors in HeLa cells and brain tissue (Fig. 1B). Immunofluorescence studies showed a prominent colocalization between p11 and 5-HT_{1B} receptors at the cell surface (Fig. 1C). The distribution of p11 mRNA in the brain resembled that of 5-HT_{1B} receptor mRNA (Fig. 1D).

Long-term administration of the tricyclic antidepressant imipramine (Fig. 2A), but not of haloperidol, risperidone, or diazepam (+6, +3, and +1% versus saline), increased the amount of p11 mRNA (+30 ± 5% versus saline) in cortex. This effect of imipramine was restricted to the forebrain, e.g., it did not occur in the raphe nuclei (–3% versus saline). In subsequent experiments, long-term administration of another antidepressant, tranylcypromine (+29 ± 4% versus saline; $P < 0.05$ Student's t test), and repeated electroconvulsive therapy (Fig. 2B) also increased the amounts of p11 mRNA in cortex. Moreover, imipramine and electroconvulsive therapy increased p11 protein in cortex (fig. S1). The amounts of p11 were compared in helpless H/Rouen mice, a genetic animal model of depression, and nonhelpless NH/Rouen mice (*11*). The amounts of p11 mRNA (Fig. 2C) and protein (fig. S1) were markedly reduced in H/Rouen mice. We also found down-regulated p11 mRNA (Fig. 2D) and protein (fig. S1) in the anterior cingulate cortex in patients who had suffered from unipolar major depression disorder.

p11 regulates the translocation of annexin II and ion channels (NaV1.8, TASK-1, TRP5/6) to the cell surface (*12*–*15*). Likewise, COS-7 cells cotransfected with 5-HT_{1B} receptors and p11 exhibited more 5-HT_{1B} receptors at the cell surface than cells transfected only with 5-HT_{1B} receptors (Fig. 3A). In contrast, the ratio of surface-to-total dopamine D_1 receptors was similar in the absence or presence of p11 (100 ± 7.4 versus 103 ± 13.0). We determined whether cotransfection with p11 would enhance the signaling efficacy of 5-HT_{1B} receptors, which are negatively coupled to adenylyl cyclase. Serotonin counteracted forskolin-induced adenosine 3′,5′-monophosphate (cAMP) formation more efficiently in COS-7 cells expressing both 5-HT_{1B} receptors and p11 than in cells expressing only 5-HT_{1B} receptors (Fig. 3B).

Because antidepressant treatments elevated p11, we investigated whether increased amounts of p11 would affect behaviors relevant to antidepressant drug action. Transgenic mice with doxycycline-regulatable overexpression of p11 under the calcium/calmodulin-dependent protein kinase II (CamKII) promoter were generated. In the absence of doxycycline, transgenic mice had elevated p11 in neurons that do not contain serotonin in the forebrain, but not in serotonin neurons in the raphe nuclei (fig. S2). These mice had increased functional 5-HT_{1B} receptors in substantia nigra (fig. S3) and exhibited reduced thigmotaxis (an index of anxiety-related distress) (Fig. 3C) and increased horizontal activity (fig. S4) in the open-field test. They also showed a decreased immobility in the tail suspension test (an index of depression-like state) (Fig. 3D). Thus, mice overexpressing p11 acted as if they were treated with antidepressants, although a confounding factor was that they appeared to be generally hyperactive. Transgenic mice treated with doxycycline had normalized p11 expression (fig. S4) and no significant alterations of thigmotaxis (Fig. 3C), immobility (Fig. 3D), or horizontal activities (fig. S4).

We also generated p11 knockout (KO) mice (fig. S5). Autoradiographic ligand-binding experiments showed that there were fewer binding sites for the 5-HT_{1B} receptor antagonist radioligands [^{125}I]iodocyanopindolol (Fig. 4A; fig. S6) and [^{3}H]GR125743 (fig. S6) in globus pallidus in p11 KO than in wild-type mice. Similarly, [^{125}I]iodocyanopindolol binding was lower in substantia nigra pars reticulata in p11 KO than in wild-type mice (77.3 ± 5.8 versus 98.8 ± 6.2 fmol/mg protein; $P < 0.05$ Student's t test). There was no difference in the affinity of serotonin to displace bound [^{125}I]iodocyanopindolol between wild-type and p11 KO mice [median effective concentration (EC_{50}) values: 57 versus 52 nM). No differences in the amounts of 5-HT_{1A}, D_1, or D_2 receptors were detected between the wild-type and p11 KO mice (fig. S6). [^{125}I]Iodocyanopindolol binding was also reduced in H/Rouen mice versus NH/Rouen mice (fig. S7).

The reduced number of 5-HT_{1B} receptors at the cell membrane in p11 KO mice was reflected in a reduced ability of the 5-HT_{1B} receptor agonist anpirtoline (*16*) to increase [^{35}S]guanosine 5′-*O*-(3′-thiotriphosphate (GTP-γ-S) binding in globus pallidus in these mice (Fig. 4B). In contrast, there was no difference in [^{35}S]GTP-γ-S binding by 8-OH-DPAT [(+/–)-8-hydroxy-2-(di-*n*-propylamino) tetralin], a 5-HT_{1A} receptor agonist, in wild-type and p11 KO mice (6.0 ± 2.1 versus 5.0 ± 2.0 optical density units). The decreased number of functional 5-HT_{1B} receptors at the cell surface of p11 KO mice was also reflected in a loss of ability of serotonin and of anpirtoline to down-regulate phospho-Thr^{202}/Tyr^{204}– ERK1/2 (extracellular signal–regulated kinase) levels in primary cortical cultures from p11 KO mice (Fig. 4C) and of anpirtoline to decrease phospho-Ser^9–synapsin I, a site phosphorylated by cAMP-dependent protein kinase, in striatal slices from p11 KO mice (Fig. 4D).

Serotonin, via 5-HT_{1B} receptors, reduces glutamate release at terminals of neurons originating from the cerebral cortex and inhibits synaptic transmission at corticostriatal synapses (*17*). We monitored the amplitude of field excitatory postsynaptic potentials (fEPSPs) evoked by brief electrical stimulation of glutamatergic fibers and recorded extracellularly in the nucleus accumbens. fEPSPs were mediated by AMPA receptors activated by endogenous glutamate released by electrical stimulation of the slice in both wild-type and p11 KO mice [fEPSP/population spike (PS) reduction 77 and 81%, respectively, compared with baseline, 15 min after the AMPA receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX)]. When applied in the perfusion solution, serotonin depressed the amplitude of the fEPSP/PS in slices from wild-type, but not from p11 KO, mice (Fig. 4E).

5-HT_{1B} receptors act as autoreceptors and inhibit serotonin release (*2*, *7*). Because p11 is expressed in the raphe nuclei, the amounts of serotonin and its major metabolite 5-hydroxyindoleacetic acid (5-HIAA) were measured in projection areas, namely, cortex, striatum, and hippocampus in wild-type and p11 KO mice. In accordance with a negative regulation of 5-HT turnover and/or metabolism by 5-HT_{1B} receptors, and a potentiating role of p11 on 5-HT_{1B} receptor function, p11 KO mice have increased levels of serotonin turnover and/or metabolism (Fig. 4F).

To evaluate behavioral effects of p11 deletion, we compared thigmotaxis in wild-type and p11 KO mice under basal conditions and in response to anpirtoline in drug-naïve mice and in mice that had been treated long-term with imipramine. In animals treated with imipramine, anpirtoline caused a significant reduction in thigmotaxis in wild-type mice, but not in p11 KO mice (Fig. 4G). In addition, there was less thigmotaxis in saline-injected wild-type than p11 KO mice (Fig. 4G). Drug-naïve wild-type and p11 KO mice exhibited similar thigmotaxis either in the absence or presence of anpirtoline. There was an increased immobility in the tail suspension test in p11 KO mice compared with wild-type mice, both under baseline conditions and after acute treatment with either anpirtoline or imipramine (Fig. 4H). These behavioral results indicate that p11 KO mice exhibit a depression-like phenotype and that p11 mediates behavioral responses to imipramine via 5-HT_{1B} recep-

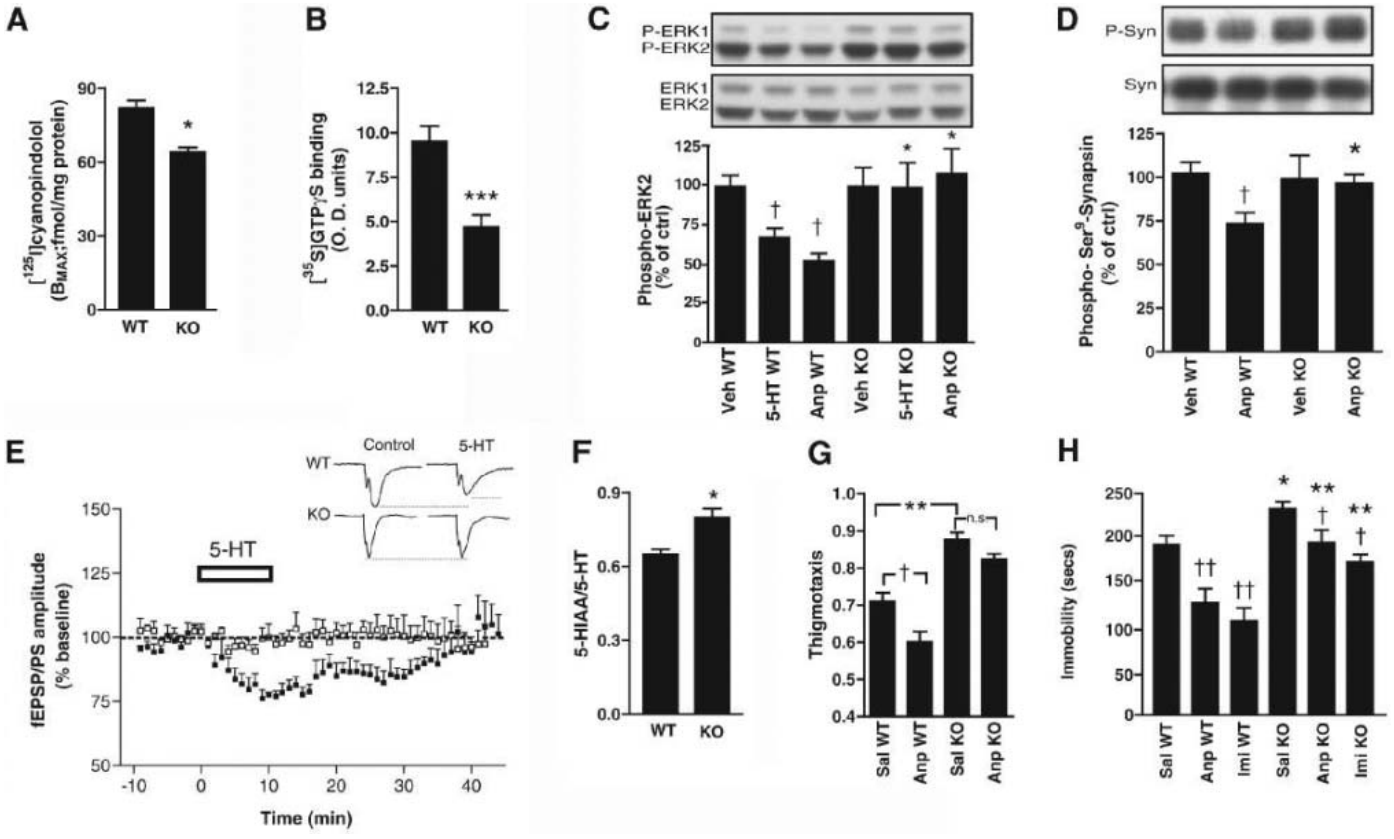

Fig. 4. Comparison of biochemical, electrophysiological, and behavioral responses in wild-type versus p11 KO mice. (**A**) Maximum specific binding (B_{max}) values for [^{125}I]iodocyanopindolol binding to 5-HT$_{1B}$ receptors in globus pallidus in wild-type and p11 KO mice. (**B**) Anpirtoline (50 μM)-stimulated [^{35}S]GTP-γ-S binding in globus pallidus in wild-type and p11 KO mice. For (A and B), data represent means ± SEM for five to eight mice per group. (**C**) Regulation of phospho-Thr^{202}/Tyr^{204}–ERK1/2 by serotonin (10 μM) and anpirtoline (10 μM) in primary cortical cultures of wild-type and p11 KO mice. (**D**) Regulation of phospho-Ser^{9}–synapsin I by anpirtoline (50 μM) in striatal slices from wild-type and p11 KO mice. For (C and D), data represent means ± SEM for three experiments, each in triplicate. (**E**) Ability of serotonin (10 μM) to inhibit corticoaccumbal glutamatergic synaptic transmission seen in wild-type mice (filled symbols) is significantly attenuated in p11 KO mice (open symbols). Data represent means ± SEM for five slices per group. (**F**) Serotonin turnover (5-HIAA/5-HT ratio) in striatal tissue is increased in p11 KO mice as compared with wild-type mice. Data represent means ± SEM for eight mice per group. (**G**) Thigmotaxis in the open field in wild-type and p11 KO mice treated long-term with imipramine (10 mg/kg per day, i.p., for 4 weeks) and challenged with saline or anpirtoline (5 mg/kg, i.p.). Data represent means ± SEM for 12 to 16 mice per group. (**H**) Behavioral analysis in the tail suspension test in wild-type and p11 KO mice treated acutely with saline, anpirtoline (5 mg/kg, i.p.), or imipramine (10 mg/kg, i.p.). Data represent means ± SEM for 14 to 16 mice per group. (A, B, F) *$P < 0.05$, ***$P < 0.001$ versus respective control by Student's t test. (C, D, G, H) *$P < 0.05$, **$P < 0.01$ versus respective wild-type group; n.s., nonsignificant, †$P < 0.05$, ††$P < 0.01$ versus respective control group by two-way ANOVA followed by Newman-Keul's test.

tors. In further support of a depression-like phenotype of p11 KO mice, we found that p11 KO mice consumed less of a palatable 2% sucrose solution than their wild-type littermates (1.74 ± 0.07 versus 2.17 ± 0.11 ml/g body weight per day; $P < 0.05$ Student's t test), which indicated a decreased responsiveness to sweet reward. Water intake was similar in the p11 KO mice and their wild-type littermates (1.51 ± 0.05 versus 1.42 ± 0.05 ml/g body weight per day), which ruled out a role of altered fluid balance in this behavior.

Taken together, the results of the present study indicate that the dynamic modulation of 5-HT$_{1B}$ receptor function by p11 may be involved in molecular adaptations occurring in neuronal networks that are dysfunctional in depression-like states.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/311/5757/77/DC1
Materials and Methods
Figs. S1 to S7
References

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Coevolved Crypts and Exocrine Glands Support Mutualistic Bacteria in Fungus-Growing Ants

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Attine ants engage in a quadripartite symbiosis with fungi they cultivate for food, specialized garden parasites, and parasite-inhibiting bacteria. Molecular phylogenetic evidence supports an ancient host-pathogen association between the ant-cultivar mutualism and the garden parasite. Here we show that ants rear the antibiotic-producing bacteria in elaborate cuticular crypts, supported by unique exocrine glands, and that these structures have been highly modified across the ants' evolutionary history. This specialized structural evolution, together with the absence of these bacteria and modifications in other ant genera that do not grow fungus, indicate that the bacteria have an ancient and coevolved association with the ants, their fungal cultivar, and the garden parasite.

Attine ants are a New World tribe having obligate associations with fungi that they cultivate for food. The ants' fungal gardens are host to specialized and virulent parasitic microfungi in the genus *Escovopsis* (Ascomycota, Hypocreales) (*1*–*3*). Infected colonies experience a significant reduction in garden growth rate and production of new workers, and under some conditions *Escovopsis* can completely overgrow the fungus garden (*1*, *2*). The symbiotic association between attine ants, their fungal cultivars, and the specialized garden parasite *Escovopsis* originated about 50 to 65 million years ago and has subsequently been shaped by millions of years of coevolution (*4*–*6*). The ant-cultivar-*Escovopsis* host-pathogen coevolution has resulted in ancient evolutionary congruence: Specific groups of attine ants are specialized on specific groups of cultivated fungi, and these fungi are host to specific groups of *Escovopsis* parasites (*4*). In addition, even at the finer phylogenetic level, there is parasite specialization on fungal cultivar genotypes (*7*).

To help defend their cultivar from the garden parasite, attine ants have a mutualistic association with filamentous bacteria that produce antibiotics with potent antagonistic properties against *Escovopsis* (*3*, *8*, *9*). The filamentous bacteria are in the genus *Pseudonocardia* (*10*); belonging in the order Actinomycetales, a group well known for its ability to produce antibiotics (*11*). *Pseudonocardia* bacteria are associated with all attine-ant species examined, and occur on specific locations on the cuticle of a given ant species. The bacterium is carried by gynes (female reproductive ants) on their mating flights and is thereby transmitted from parent to offspring colonies (*8*). Individual ant nests are associated with a single strain of *Pseudonocardia*, but genetically distinct strains

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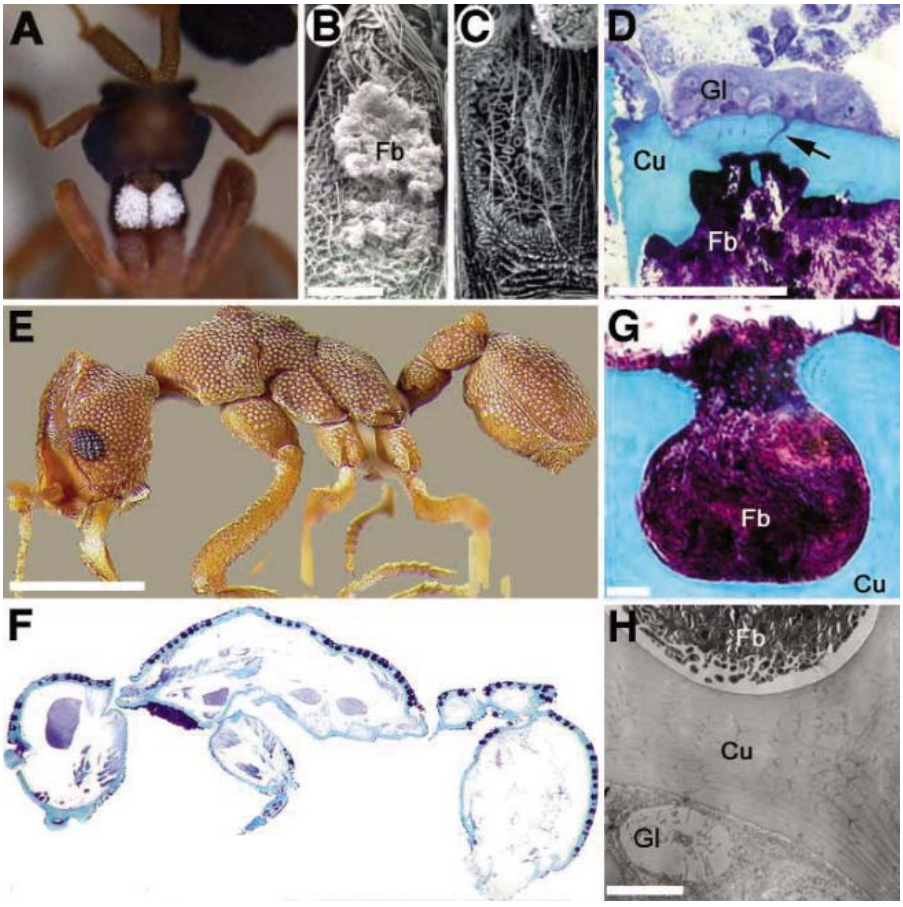

Fig. 1. (**A**) Photograph of *Cyphomyrmex costatus* showing the bacteria on the propleural plates. SEM of the plates in *C. muelleri*: The left plate is covered with bacteria (**B**), whereas they have been removed from the right plate, revealing the underlying fovea (**C**). (**D**) Light micrograph of a semithin cross section through the propleural plate of *C. longiscapus* showing the gland (Gl) and duct cells (black arrow) associated with the fovea and the bacterium (Fb) on the plate (Cu for cuticle). (**E**) Photograph of *C. longiscapus*, illustrating foveae openings covering most of the cuticle. (**F**) Sagittal semithin section through a *C. longiscapus* worker, illustrating foveae outlining nearly the entire body of the ant. (**G**) Light micrograph of a single fovea within the cuticle (Cu) illustrating the abundance of mutualistic bacteria (Fb) within the crypt. (**H**) TEM of the lower section of a fovea showing a single glandular cell (Gl) and bacteria (Fb) within the crypt. Scale bars: 50 μm (A to C), 5 μm (E and G), and 0.5 mm (F). [Photograph in (A) by A. Little]

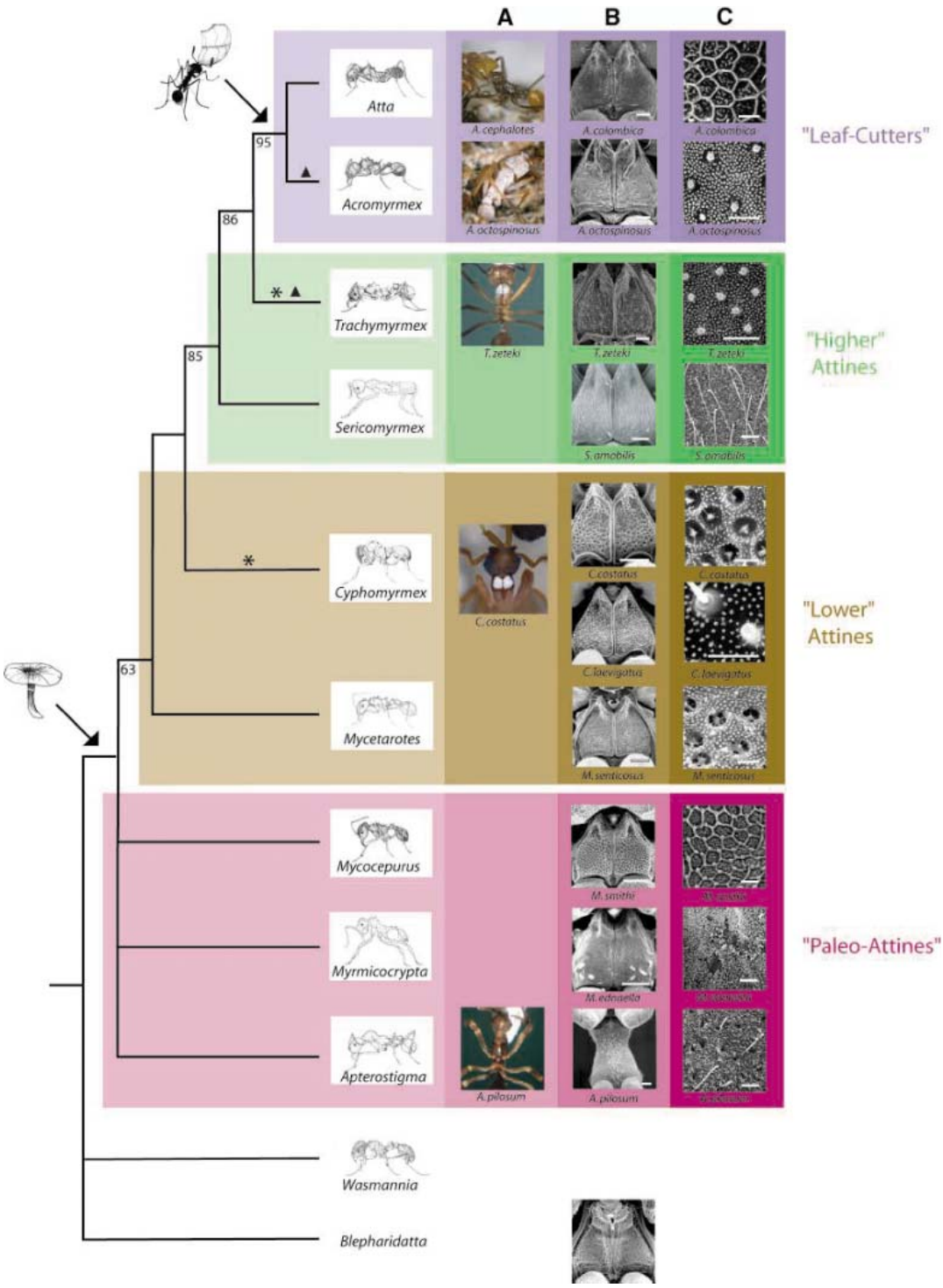

Fig. 2. Genus level phylogeny of fungus-growing ants [adapted from (*15*, *16*)] illustrating the location and modifications of the exoskeleton for maintaining the mutualistic bacteria. The origin of fungus growing by attine ants and the leaf-cutters is represented by the Lepiotaceous mushroom and the worker carrying a leaf fragment, respectively. Major groups of attine ants are depicted by colored boxes, illustrating the phylogenetically basal genera in the "paleo-attines" (red), the "lower" attine genera (brown), the "higher" attines (green), and the leaf-cutters (blue). (Column A) Photographs illustrate the location of the bacterium under the forelegs in the paleo-attines, on the propleural plates in the "lower" and "higher" attines, the presence all over the integument in the genus *Acromyrmex*, and absence on the cuticle in *Atta*. (Column B) SEM micrographs of the location of the bacterium, under the forelegs in *Apterostigma* and on the propleural plates in other groups. (Column C) SEM micrograph close-ups for the structures presented in (B), showing the specific structural modifications for different groups of fungus-growing ants. Presence of foveae (star) and tubercles (triangle) all over the body in some species within a genus are indicated by the corresponding symbol above the branch on the phylogeny. Scale bars: 0.5 mm (B), 10 μm (C). [The line drawings of *Wasmannia auropunctata*, *Cyphomyrmex rimosus*, *Trachymyrmex septentrionalis*, *Acromyrmex versicolor*, and *Atta texana* were made by Smith (*20*); those of *Myrmicocrypta ednaella* and *Sericomyrmex amabilis* were made by Weber (*21*); and those of *Apterostigma pilosum*, *Mycocepurus smithi*, and *Mycetarotes* sp. were made by A. Little. Photographs of *Acromyrmex octospinosus* and *Cyphomyrmex costatus* in (A) were taken by A. Little.]

and/or species of bacteria can occur within populations of the same species and between species of ants (*12*). The diversity and mode of transmission predict congruence between the ant and bacteria phylogenies; however, the complete evolutionary history of ant-associated *Pseudonocardia* still remains to be determined. Here we examine the presence and evolution of specific cuticular structures on attine ants to house and maintain the parasite-inhibiting bacteria (*8*).

To investigate this, we first examined ant species in the genus *Cyphomyrmex* because of the conspicuous white "bloom" of bacterium present on the propleural plates (Fig. 1A). Scanning electron microscopy (SEM) of *Cyphomyrmex longiscapus* and *C. muelleri* workers with the filamentous bacterium removed revealed the presence of a previously unnoticed large crescent-shaped cavity (fovea) on each propleural plate (*13*) (Fig. 1, B and C; fig. S1A). The foveae are porous and occupy a significant proportion of the surface area of the propleural plates; the filamentous bacteria grow directly within these crypts (Fig. 1C).

Our investigations further revealed, in the semithin sections of the propleural plates in *C.*

longiscapus, the presence of a previously unknown exocrine gland located on the inner surface of the cuticle, just below the foveae. The gland consists of bicellular units, each formed by a gland cell and duct cell (*14*). The duct cells cross the cuticle and open within the foveae where the bacteria are cultured (Fig. 1D; fig. S1, A to C).

In addition to foveae occurring on the propleural plates, *C. longiscapus*, *C. muelleri*, and *C. costatus* ants also have bacteria-filled foveae covering most of the surface of worker exoskeletons, including the head, thorax, abdomen, and legs (Fig. 1, E to G). These crypts have small openings to the external surface of the ant, with minute microtrichia (hair-like cuticular projections) that appear to shield the opening of the crypt (fig. S1D). At the bottom of each fovea is a porous tubercle (integumental protrusion) (fig. S1E), connected via a duct cell to the corresponding gland cell directly beneath the crypt (Fig. 1H).

The locality of bacteria on the cuticle varies across fungus-growing ant species (Fig. 2, column A). Examination of specialized structures for bacterial maintenance across the phylogenetic diversity of attine ants revealed several broad evolutionary patterns (Fig. 2). Ant genera closely related to attine ants, *Wasmannia* and *Blepharidatta* (*15*, *16*), do not have filamentous bacteria, fovea, or tubercles (Fig. 2). In the most phylogenetically basal attine ants (paleoattines), such as the genus *Apterostigma*, the filamentous bacterium occurs on the mesopleura (under the forelegs), where it grows directly on the cuticle over the pores of duct cells connected to the corresponding gland cells (Fig. 2, fig. S1F). In most species of "lower" attine ants, mutualistic bacteria occur on the propleural plates (e.g., *Cyphomyrmex costatus*, in Fig. 2), in which the bacterium grows on tubercles within foveae. Similarly, the bacteria are also concentrated on the propleural plates in the "higher" attine genus *Trachymyrmex* and the leaf-cutter genus *Acromyrmex*, although in these two genera the bacteria grow on gland cell–associated tubercles directly on the exoskeleton rather than in foveae (Fig. 2).

Several species of plants and animals engaged in mutualistic associations with microbes have evolved structures to house their symbionts. For example, root nodules in legumes house *Rhizobium*, squid light organs are filled with bioluminescent bacteria, aphids have modified bacteriocytes that form organlike structures to rear *Buchnera*, and some beetles and woodwasps have specialized structures (known as mycangia) to house mutualistic fungi (*17*–*19*). Our findings indicate that the exoskeleton of attine ants is modified to house mutualistic bacteria, apparently supporting their growth through glandular secretions. In addition, our phylogenetic examination of the structures across the fungus-growing ant tribe revealed that, like the cultivar and garden parasite, the mutualistic *Pseudonocardia* bacteria was apparently present at the earliest stages of fungus cultivation by ants. This is supported by the presence of the bacteria and bacteria-associated glands and duct cells in the most phylogenetically basal genera (e.g., *Apterostigma)*, in contrast to their absence in closely related ants that do not cultivate fungus gardens (*Blepharidatta* and *Wasmannia).*

The apparently early evolutionary origin of the bacteria within the fungus-growing ant symbiosis, in combination with bioassay results confirming that filamentous bacteria isolated from across the phylogenetic diversity of attine ants are effective at inhibiting their corresponding garden parasites (*8*, *10*, *13*), indicate that the bacteria have provided an efficient defense against *Escovopsis* for millions of years. This raises the question of how the antibiotics have remained effective without rampant evolution of resistance in the parasite over the long evolutionary history of this symbiosis.

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Materials and Methods
SOM Text
Figs. S1 and S2
References

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A Clonogenic Bone Marrow Progenitor Specific for Macrophages and Dendritic Cells

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Macrophages and dendritic cells (DCs) are crucial for immune and inflammatory responses and belong to a network of cells that has been termed the mononuclear phagocyte system (MPS). However, the origin and lineage of these cells remain poorly understood. Here, we describe the isolation and clonal analysis of a mouse bone marrow progenitor that is specific for monocytes, several macrophage subsets, and resident spleen DCs in vivo. It was also possible to recapitulate this differentiation in vitro by using treatment with the cytokines macrophage colony-stimulating factor and granulocyte-macrophage colony-stimulating factor. Thus, macrophages and DCs appear to renew from a common progenitor, providing a cellular and molecular basis for the concept of the MPS.

Macrophages (MΦs) and dendritic cells (DCs) are involved in the scavenging of dying cells, pathogens, and molecules through phagocytosis and endocytosis and the use of pattern recognition receptors (*1*). As a result, both cell types make a vital contribution to immunity and inflammatory responses to pathogenic microorganisms (*2*).

At the same time, these cells are distinct: MΦs represent scavenging tissue-resident cells and take part in the innate immune response (*3*), whereas DCs represent professional antigen-presenting cells that trigger and regulate the adaptive immune response (*4*). Both lineages also each display a remarkable heterogeneity in phenotype, tissue localization, and function and have been divided into several subsets (*5*).

Although the origin and renewal of MΦs and DCs have been intensively investigated, the lineage relation between these cells types is unclear (fig. S1). Most MΦs are dependent on macrophage colony-stimulating factor (M-CSF) for their development in vitro and in vivo, whereas most DC subsets are not (*6*). Conversely, the ligand for the receptor tyrosine kinase Flk-2 (FLT3-L) is important for the development of many DC subsets but appears not to be required for MΦ development (*7*). MΦs are believed to derive solely from myeloid progenitors, but recent in vivo experiments have shown that most steady-state DC subsets, including CD11c$^+$ CD8α$^-$, CD11c$^+$ CD8α$^+$ DCs, and plasmacytoid DCs (PDCs), can differentiate from early bone marrow (BM) progenitors such as the common lymphoid progenitors (CLPs) as well as the common myeloid progenitors (CMPs) (*8*–*12*). From these and other reports, it has been hypothesized that MΦs and DCs have distinct progenitors (*11*, *13*).

However, an alternative hypothesis is that many DC and MΦ subsets derive from a common precursor able to develop into either cell type depending on cytokine signals or other cues encountered at tissue sites (*14*). This hypothesis of a common progenitor shared by cells of the mononuclear phagocyte system (MPS) (*15*, *16*) is supported by the capacity of human and mouse monocytes and recently described mouse pre-immunocytes to give rise to MΦs and DCs in vitro (*17*–*20*). Furthermore, mouse blood monocytes can differentiate in vivo into a particular subset of antigen-presenting DCs under inflammatory conditions (*21*, *22*), although it is unknown whether blood monocytes also contribute to classical steady-state DC subsets, such as the spleen CD8α$^+$ and CD8α$^-$ DCs, and to tissue MΦs (*22*, *23*).

In a search for progenitors specific for MΦs and DCs, we identified a mouse BM population that expresses both CD117 (c-kit, the receptor for stem cell factor) and the chemokine receptor CX_3CR1 but not markers of lineage-committed precursors (Lin$^-$) (Fig. 1A) (*24*). CX_3CR1 is widely expressed among monocytes, DCs (*22*, *25*), and MΦs (fig. S2), and its expression can be easily followed with the use of a reporter system in which green fluorescent protein (GFP) is driven at the locus of the *Cx$_3$cr1* gene in mice (*22*, *25*). CX_3CR1^+ CD117$^+$ Lin$^-$ cells represented ~0.5% of total BM cells and could be highly purified (>99%) by using flow cytometry fluorescence-activated cell sorting (FACS) on

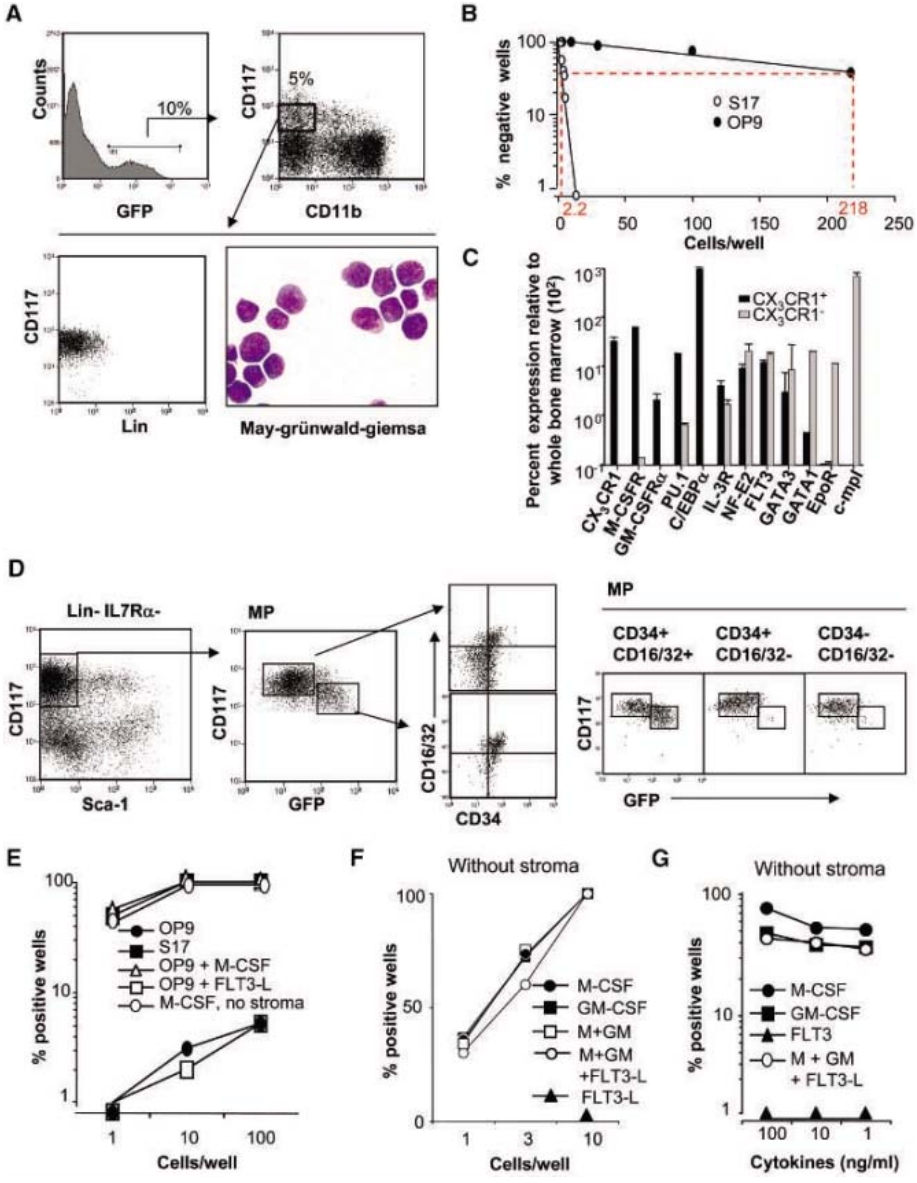

Fig. 1. Isolation of a CX_3CR1^+ clonogenic proliferating BM progenitor. (**A**) BM cells expressing GFP and CD117 but not CD11b (top right) CD3, CD19, NK1.1, Ia^b, CD11c, B220, TER-119, or Gr1 (Lin; bottom left) were purified and stained with MGG (bottom right). (**B**) Cloning efficiency was assessed by limiting dilution series on S17 (open circles) or OP9 (solid circles) stromal cells. (**C**) Real-time polymerase chain reaction analysis of gene expression was performed for CX_3CR1^+ CD117$^+$ (black) and CX_3CR1^- CD117$^+$ (gray). (**D**) Lin$^-$ IL7Rα$^-$ CD117$^+$ Sca-1$^-$ cells (MPs) were purified from BM and analyzed for expression of GFP, CD16/32, and CD34. (**E**) CX_3CR1^+ CD117$^+$ Lin$^-$ cells (solid squares) or OP9 cells in the absence (solid circles) or presence of exogenous M-CSF (open triangles) or FLT3-L (open squares), or in the presence of M-CSF alone (open circles) were plated at 1, 10, or 100 cells per well onto S17. (**F** and **G**) Cells were plated in the absence of stroma at varying cell numbers per well (E) and at one cell per well (F) in the presence of M-CSF (solid circles), GM-CSF (solid squares), M-CSF and GM-CSF (open squares), M-CSF and GM-CSF and FLT3-L (open circles), or FLT3-L (solid triangles).

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the basis of the expression of GFP and CD117 and the absence of expression of CD11b (Fig. 1A). Morphology of these cells appeared to parallel immature myeloid progenitors (Fig. 1A).

A cloning efficiency of CX_3CR1^+ $CD117^+$ Lin^- cells was calculated as 50%, as determined by limiting dilution analysis (Fig. 1B) and by single-cell sorting followed by culturing on S17 stromal cells (*26*) (fig. S3A). Clones expanded exponentially in culture to colonies of 3×10^3 to 1×10^4 cells after 7 days, indicating that each proliferating progenitor had undergone an average of 12 mitoses (fig. S3B).

mRNA for the M-CSF receptor *c-fms*, the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor α chain, and the transcription factor CEBPα were enriched by a factor of 100 to 1000 in the CX_3CR1^+ $CD117^+$ Lin^- cells as compared with $CD117^+$ Lin^- progenitor cells depleted of CX_3CR1-expressing cells (Fig. 1C). Genes usually associated with lymphoid progenitors such as *Gata3*, *Flt3*, and *Pu.1* were also expressed, in contrast to no or weak expression of genes associated with the erythrocyte-megakaryocyte pathway *Gata1*, *Epo-R*, and *c-mpl* (Fig. 1C).

CX_3CR1^+ $CD117^+$ Lin^- cells existed within the $CD117^+$ $Sca1^-$ $IL7R\alpha^-$ myeloid progenitors (MPs) (*8*) (Fig. 1D). CX_3CR1^+ $CD117^+$ Lin^- cells homogenously expressed CD34 and CD16/32, a phenotype shared by granulocyte-macrophage progenitors (GMPs) found among MPs (*8*) (Fig. 1D). However, they could be distinguished from GMPs by lower expression of CD117 and elevated expression of CX_3CR1 (Fig. 1D).

The efficiency of cloning CX_3CR1^+ $CD117^+$ Lin^- cells by culturing on M-CSF-deficient stromal cells [OP9 cells (*27*)] was reduced by two orders of magnitude compared with the efficiency of cells cultured on S17 cells (Fig. 1B). Addition of recombinant M-CSF completely restored cloning efficiency (Fig. 1E), and recombinant GM-CSF could substitute for this effect. Furthermore, stroma was dispensable for the growth of both M-CSF and GM-CSF cultures but not FLT3-L cultures of progenitors (Fig. 1, F and G). Lastly, an additive effect of M-CSF and GM-CSF on cloning efficiency was not observed (Fig. 1, F and G), suggesting that the cytokines were acting on the same cell.

In contrast to sorted CX_3CR1^- $CD117^+$ Lin^- cells, which gave rise to colonies of polymorphonuclear cells (PMN), MΦs, and DCs; nearly all colonies (96%) arising from single CX_3CR1^+ $CD117^+$ Lin^- cells grown on S17 stroma possessed morphology typical of MΦs and DCs but not PMN (Fig. 2A). Limiting dilution analysis showed that CX_3CR1^+ $CD117^+$ Lin^- cells were also devoid of B or natural killer (NK) lymphoid potential (fig. S4A). When grown in the absence of stroma, clonal colonies cultured with M-CSF expressed CX_3CR1, appeared macrophage-like by morphology and phenotype ($CD11b^+$ $CD11c^-$) (Fig. 2B), and were efficient at phagocytosing heat-killed *Escherichia coli* (fig. S4B). Colonies cultured with GM-CSF down-regulated CX_3CR1, had the morphology and phenotype of DCs ($CD11b^{int}$ $CD11c^+$) (Fig. 2B), and were capable of processing and presenting a model antigen (ovalbumin) to naïve T cells (fig. S4C). Notably, single cells cloned in the presence of both cytokines gave rise to both macrophage- and DC-like cells (Fig. 2B). Addition of FLT3-L to GM-CSF did not significantly modify CX_3CR1, CD11b, or CD11c expression (fig. S5).

In order to test the in vivo potential of CX_3CR1^+ $CD117^+$ Lin^- cells, we intravenously transferred 2×10^4 cells purified from *Cd45.2* donor mice with the use of FACS to irradiated congenic *Cd45.1* C57BL/6 recipient mice (Fig. 3A). Donor-derived cells first became detectable in the spleen at day 2, expressed intermediate amounts of GFP, and were $CD45.2^+$ $CD11b^{int}$ $CD11c^-$ (Fig. 3B). By day 7, three new populations of donor-derived spleen cells were easily detectable: $CD11b^-$ $CD11c^+$, $CD11b^+$ $CD11c^+$, and $CD11b^+$ $CD11c^-$ (Fig. 3B). In contrast, we did not detect donor-derived $Gr1^{hi}$ PMNs, $B220^+$ B cells, $CD3^+$ T cells, $NK1.1^+$ NK cells, or $Gr1^+$ $B220^+$ PDCs in any tissues between 2 and 102 days after transfer (Fig. 3C, left, and fig. S6). The appearance of $CD11b^+$ and $CD11c^+$ cells was delayed by a week when CX_3CR1^+-depleted $CD117^+$ Lin^- progenitors were transferred in place of CX_3CR1^+ $CD117^+$ Lin^- cells (Fig. 3C, right). At day 7 after transfer, CX_3CR1^+ $CD117^+$ Lin^- cells gave rise to more donor-derived $CD11c^+$ cells than did CX_3CR1^- $CD117^+$ Lin^- cells, despite a lower prolif-

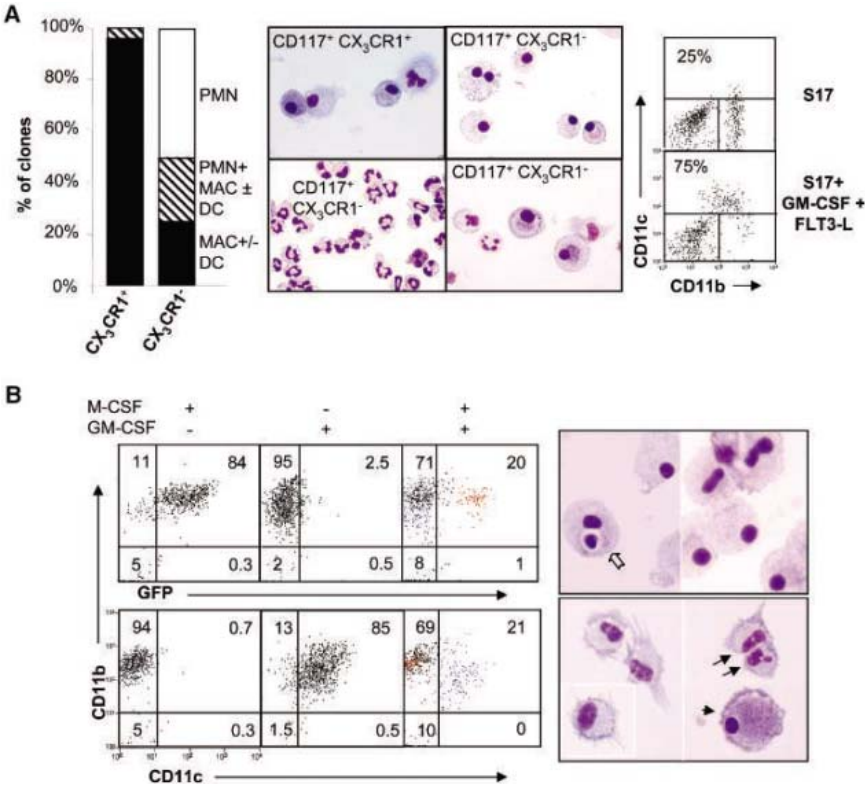

Fig. 2. Differentiation of CX_3CR1^+ $CD117^+$ Lin^- cells in vitro. (**A**) CX_3CR1^+ $CD117^+$ Lin^- progenitors gave rise to colonies with MΦ- and DC-like morphology (black bars and top left photo). CX_3CR1^- $CD117^+$ Lin^- progenitors gave rise to colonies of PMN (open bars and bottom left photo), colonies of MΦ and DC (black bars and top right photo), and colonies of MΦ and DC plus PMN (hatched bars and bottom right photo). (Right) CD11b and CD11c expression on colonies from single cells cultured on S17 cells with exogenous GM-CSF and FLT-3L compared with those cultured on S17 cells alone. S17 cells appear as $CD11b^-$ $CD11c^-$. (**B**) CX_3CR1^+ $CD117^+$ Lin^- cells cultured without stroma but in the presence of M-CSF (left profiles and top photos) or GM-CSF (middle profiles and bottom left photo) or both (right profiles and bottom right photo). M-CSF cultures display macrophage-like phenotype and morphology, including phagocytosis of dead cells (open arrow), whereas GM-CSF cultures display DC-like phenotype and morphology (bottom left photos). In the presence of both cytokines (bottom right photo), macrophage- and DC-like cells (arrowhead and arrows, respectively) are observed.

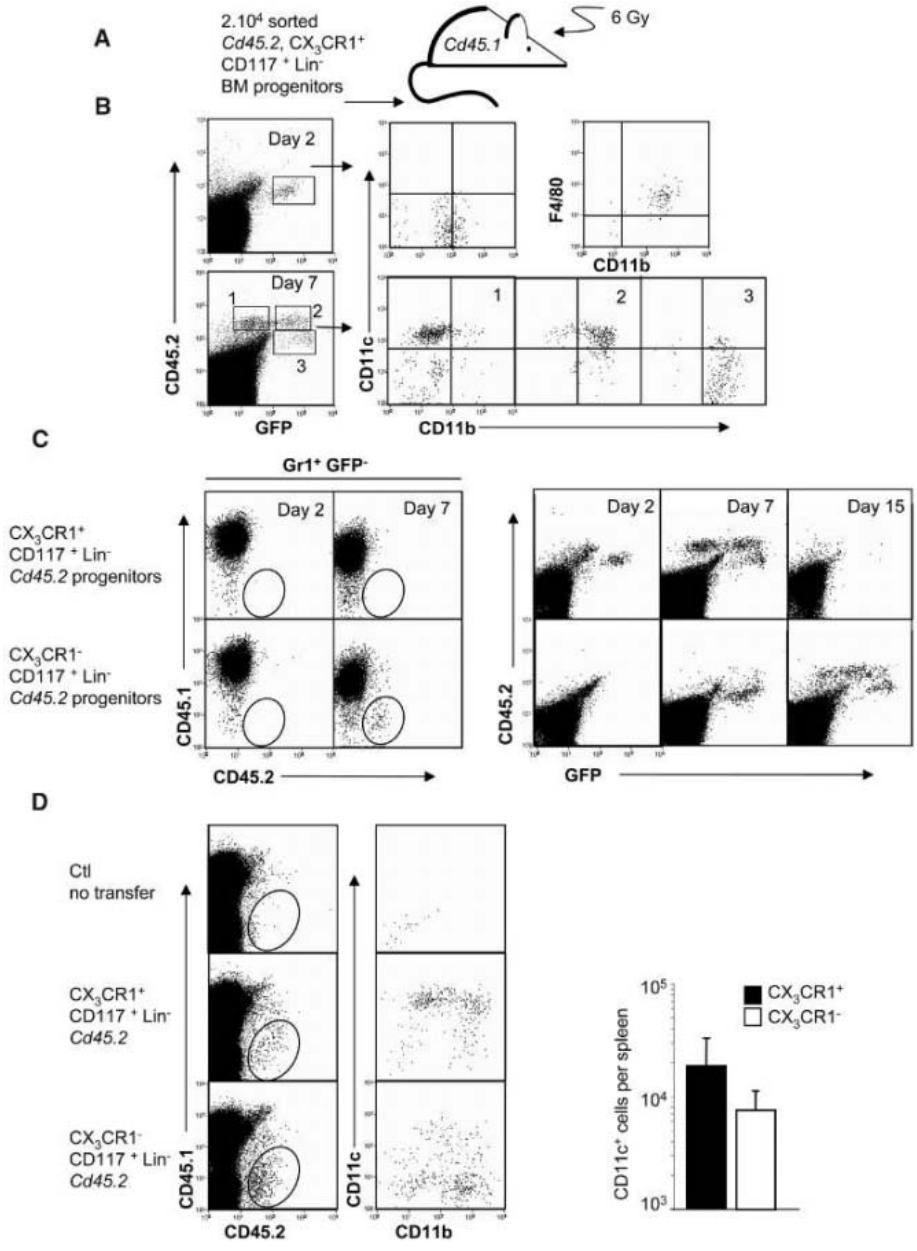

Fig. 3. Differentiation of CX_3CR1^+ $CD117^+$ Lin^- cells in vivo. (**A**) Sorted CX_3CR1^+(GFP^+) $CD117^+$ Lin^- cells (2×10^4) from mice expressing CD45.2 were transferred intravenously into irradiated (6 gray) wild-type congenic mice expressing CD45.1. (**B**) Donor-derived spleen cells ($CD45.2^+$ $GFP^{+/-}$, left) were analyzed for expression of CD11b, F4/80, and CD11c (right) 2 days (top) or 7 days (bottom) after transfer. (**C**) Sorted progenitors ($CD117^+$ Lin^- cells), expressing CX_3CR1 (top) or not (bottom), were transferred into recipient mice, and spleen cells were harvested at various times after transfer and analyzed by FACS. Donor-derived ($CD45.1^-$ $CD45.2^+$) $Gr1^+$ GFP^- cells (PMN) were detectable 7 days after transfer of CX_3CR1^- progenitors but not CX_3CR1^+ progenitors (left). $CD11b^+$ and/or $CD11c^+$ cells were analyzed for donor origin (CD45.2 and GFP expression) between 2 and 15 days after transfer (right). (**D**) Seven days after transfer, donor-derived cells ($CD45.1^-$ $CD45.2^+$, left) from CX_3CR1^- progenitors were mostly $CD11c^-$, whereas those from CX_3CR1^+ progenitors were mostly $CD11c^+$ (middle) and were the major source of spleen $CD11c^+$ cells (right).

eration potential (Fig. 3D and fig. S3B). These data indicate that the CX_3CR1^+ $CD117^+$ subset was the main progenitor intermediate for donor-derived $CD11b^+$ and $CD11c^+$ cells in vivo.

Donor-derived $CD11c^+$ cells were detectable in the spleen of recipients beginning at day 4 after transfer of 2×10^4 CX_3CR1^+ $CD117^+$ Lin^- cells (Fig. 4). These cells represented between 0.18 and 52.6% of total spleen $CD11c^+$ (average of 7.15%, $n = 17$). Among $CD11c^+$ cells, $CD11b^-$ cells expressed CD8α but not CX_3CR1, whereas $CD11b^+$ cells expressed CX_3CR1 but not CD8α, which is consistent with observations in mouse spleen under steady-state conditions (*25*) (Fig. 4A and fig. S7). Immunohistochemical analysis performed at day 7 after transfer confirmed the presence of donor-derived DCs in the white pulp of the spleen, surrounded by marginal sinus MΦs (Fig. 4B). The number of donor-derived DCs increased until day 6 to 7, decreasing thereafter and reaching background numbers after day 15 (Fig. 4C). Thus, both $CD8\alpha^+$ and $CD8\alpha^-$ DCs in these studies were short-lived, as suggested by previous studies (*5*, *28*), and arose from a common proliferating CX_3CR1^+ $CD117^+$ Lin^- BM progenitor with apparent limited self-renewal. BM monocytes were at least two orders of magnitude less efficient than progenitors at generating $CD8\alpha^-$ DCs after transfer, and we did not observe convincing evidence that monocytes could give rise to $CD8\alpha^+$ DCs (fig. S8). Whether inflammation was involved in the differentiation of progenitors into steady-state spleen DCs was difficult to assess. However, irradiation of the host, which causes inflammation, was not required for the differentiation of donor-derived DCs (fig. S9), further suggesting that progenitors gave rise to steady-state splenic DCs.

$F4/80^+$ GFP^+ cells were detected at day 2 by immunohistochemical analysis as scattered rounded cells in the red pulp (Fig. 4D) and likely correspond to the $F4/80^+$, $CD11b^+$ GFP^+ $CD45.2^+$ monocytes detected by flow cytometry (Fig. 3B). At time points later than 1 week after transfer, $F4/80^+$ GFP^+ MΦs were difficult to detect by FACS (most likely because of the technical difficulty of extracting MΦ tissue) but were easily identified by histology in the red pulp up to several weeks posttransfer (Fig. 4D). GFP^+ marginal sinus and marginal zone MΦs were identified on the basis of the expression of MOMA1 and of SIGN-R1 and MARCO, respectively (Fig. 4E). Lastly, donor-derived $F4/80^+$ peritoneal MΦs were detectable 3 days after thioglycollate injection (Fig. 4F), and donor-derived cells with a microglial phenotype were detectable in the brain of irradiated recipients (fig. S10). Together, these data indicate that CX_3CR1^+ $CD117^+$ Lin^- cells may be progenitors for several populations of MΦ in this experimental setting.

Previous reports described precursor populations that can generate DCs or MΦs (*14*), but their differentiation potential was not restricted to these lineages. Monocytes differentiate into $CD11c^{int}$ DCs under inflammatory conditions (*21*, *22*) but have a very limited potential to differentiate into steady-state spleen DCs in vivo (fig. S8). The novel progenitor described here and that we name MDP, for MΦ and DC progenitor, gives rise to monocytes, to several subsets of MΦs, and to steady-state $CD11c^+$ $CD8\alpha^+$ and $CD11c^+$ $CD8\alpha^-$ DCs in vivo (Fig. 4G). In contrast, the MDP is devoid of lymphoid, erythroid, and megakaryo-

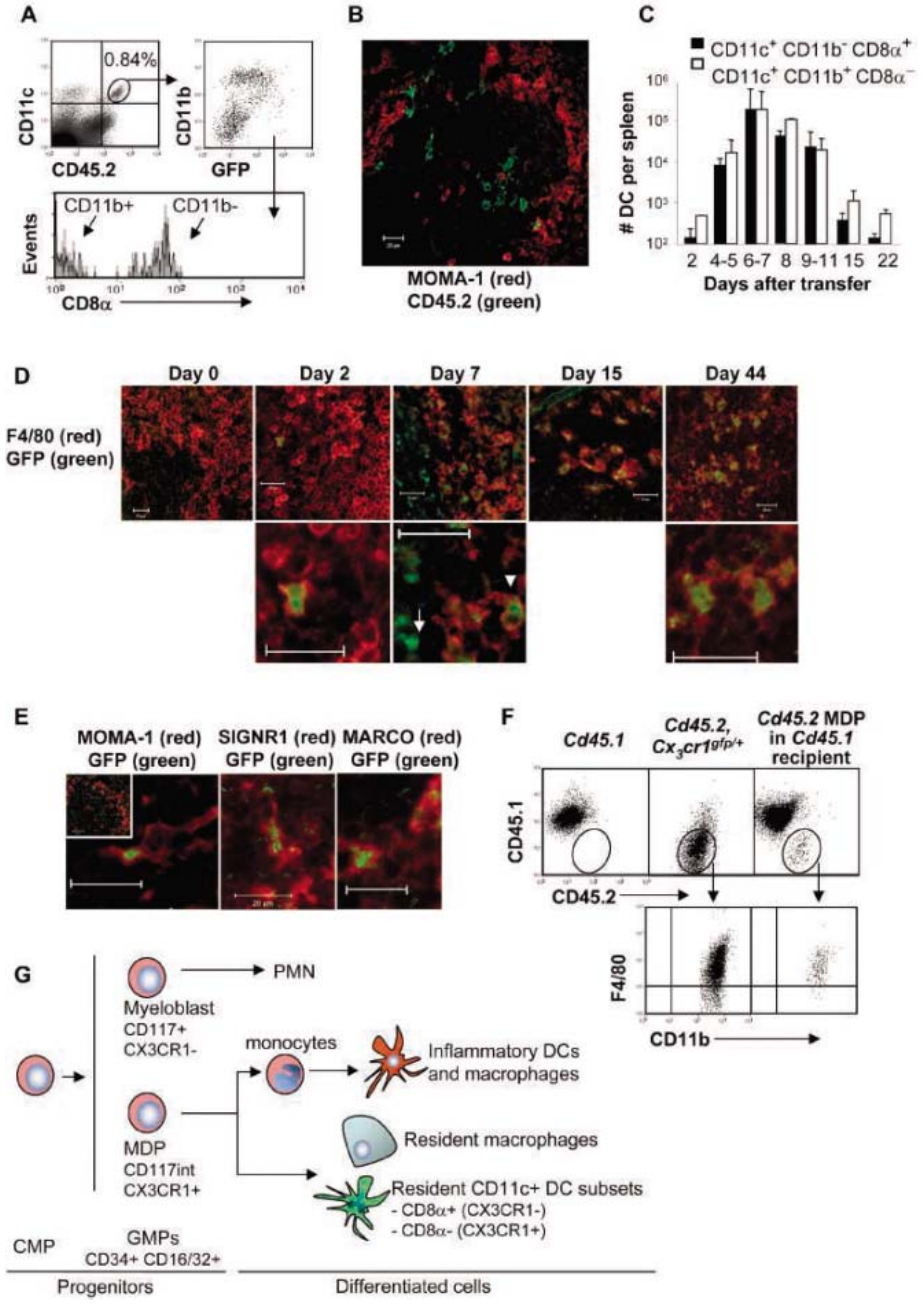

Fig. 4. Characterization of DCs and MΦs derived in vivo from CX_3CR1^+ $CD117^+$ Lin^- progenitors. (**A**) $CD45.2^+$ $CD11c^+$ cells (left) consist of $CD11b^+$ GFP^{high} (CX_3CR1^{high}) $CD8\alpha^-$ and $CD11b^-$ GFP^{low} (CX_3CR1^{low}) $CD8\alpha^+$ populations (right and bottom). (**B**) Donor-derived ($CD45.2^+$, green) cells in sections of recipient spleens stained with MOMA-1 (red). (**C**) After transfer of 2×10^4 CX_3CR1^+ $CD117^+$ Lin^- progenitors, the number of donor-derived ($CD45.2^+$ and/or GFP^+) $CD11c^+$ $CD11b^-$ cells (black) or $CD11c^+$ $CD11b^+$ cells (white) in the entire spleen (*y* axis) was estimated as described in (*24*). (**D**) Donor-derived (GFP^+, green), $F4/80^+$ (red) cells within spleens of transfer recipients. Details of the top row of photos are shown in the bottom row. At day 7, $F4/80^+$ GFP^+ (arrowhead) and $F4/80^-$ GFP^+ cells (arrow) could also be detected. (**E**) GFP^+ MΦ detected with MOMA-1 (left), SIGNR1 (middle), or MARCO (right). Scale bar is 20 μm for all images. (**F**) Thioglycolate-elicited $CD45.1^-$ $CD45.2^+$ $F4/80^+$ $CD11b^+$ MΦ were detectable in peritoneal exudates of *Cd45.2 Cx3cr1*$^{gfp/+}$ mice (middle) and *Cd45.1* mice that received 2×10^4 CX_3CR1^+ $CD117^+$ Lin^- progenitors (MΦ and DC progenitors or MDP) (right) but not controls (*Cd45.1*, left). (**G**) Summary of the proposed differentiation potential of the MDP, and its origin and relationship with other progenitors, on the basis of our current findings.

cytic potential and, reminiscent of the monoblast described by van Furth in 1975 (*29*), also lacks PMN differentiation potential. In this experimental system, we could not detect PDCs in the progeny of the MDP, suggesting that this DC subset may originate from a distinct lineage. Because the MDP can be selected or instructed to differentiate by external cues, we suggest that it might be possible to modulate differentiation toward particular MΦ or DC subsets in a therapeutic setting and thereby influence physiological and pathological processes.

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Materials and Methods
Figs. S1 to S10
Table S1
References and Notes

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Empirical Analysis of an Evolving Social Network

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Social networks evolve over time, driven by the shared activities and affiliations of their members, by similarity of individuals' attributes, and by the closure of short network cycles. We analyzed a dynamic social network comprising 43,553 students, faculty, and staff at a large university, in which interactions between individuals are inferred from time-stamped e-mail headers recorded over one academic year and are matched with affiliations and attributes. We found that network evolution is dominated by a combination of effects arising from network topology itself and the organizational structure in which the network is embedded. In the absence of global perturbations, average network properties appear to approach an equilibrium state, whereas individual properties are unstable.

Social networks have attracted great interest in recent years, largely because of their likely relevance to various social processes, such as information processing (*1*), distributed search (*2*), and diffusion of social influence (*3*). For many years, however, social scientists have also been interested in social networks as dynamic processes in themselves (*4*): Over time, individuals create and deactivate social ties, thereby altering the structure of the networks in which they participate. Social network formation is a complex process in which many individuals simultaneously attempt to satisfy their goals under multiple, possibly conflicting, constraints. For example, individuals often interact with others similar to themselves—a tendency known as homophily (*5*, *6*)—and attempt to avoid conflicting relationships (*7*, *8*) while exploiting cross-cutting circles of acquaintances (*9*). However, the realization of these intentions is subject to spatial and social proximity of available others (*9*, *10*). In circumstances where individuals may benefit from cooperative relationships, they may emphasize embedded ties—those belonging to locally dense clusters (*11*). For example, they may choose new acquaintances who are friends of friends—a process known as triadic closure (*12*). They may, however, also seek access to novel information and resources and hence benefit from access to bridges (*13*)—connections outside their circle of acquaintances—or by spanning structural holes (*14*) precisely between others who do not know one another. Finally, social ties may dissolve for various reasons, such as when they are not supported by other relations (*15*), or else conflict with them (*16*).

To what extent each of these individually plausible mechanisms manifests itself in various social and organizational contexts is largely an empirical matter, requiring longitudinal (i.e., collected over time) network data (*4*) combined with information about individuals' attributes and group affiliations (*6*, *10*, *17*). Yet longitudinal network data are rare, and the best known examples are for small groups (*4*, *18*). Recent studies of much larger networks, by contrast, have tended to focus on cross-sectional (i.e., static) analysis (*19*, *20*), or they have emphasized either the interactions between individuals (*21*, *22*) or their group affiliations (*17*), but not both.

We analyzed a longitudinal network data set created by merging three distinct but related data structures. First, we compiled a registry of e-mail interactions in a population of 43,553 undergraduate and graduate students, faculty, and staff of a large university over the course of one academic year. For each e-mail message, the timestamp, sender, and list of recipients (but not the content) were recorded. Second, for the same population, we gathered information specifying a range of personal attributes (status, gender, age, departmental affiliation, and number of years in the community). Third, we obtained complete lists of the classes attended and taught, respectively, by students and instructors in each semester. For privacy protection, all individual and group identifiers were encrypted; we can determine, for example, whether two individuals were in the same class together but not which class that was. Because in a university setting class attendance provides essential opportunities for face-to-face interaction (at least for students), we used classes to represent the changing affiliation structure.

Our use of e-mail communication to infer the underlying network of social ties is supported by recent studies reporting that use of e-mail in local social circles is strongly correlated with face-to-face and telephone interactions (*23*, *24*). Individuals and groups of individuals may differ in their e-mail usage; thus, inferences drawn on a small sample of communicating pairs may be confounded by the idiosyncrasies of particular personalities and relationships. However, by averaging over thousands of such relationships, we expect that our results will represent only the most general regularities (at least within the environment of a university community) governing the initiation and progression of interpersonal communication. To ensure that our data do indeed reflect interpersonal communication as opposed to ad hoc mailing lists and other mass mailings, we filtered out messages with more than four recipients (95% of all messages had four or fewer addressees). After filtering, there were 14,584,423 messages exchanged by the users during 355 days of observation.

Ongoing social relationships produce spikes of e-mail exchange that can be observed and counted (*20*, *21*). The stronger the relationship between two individuals, the more spikes will be observed for this particular pair, on average, within a given time interval. We approximate instantaneous strength w_{ij} of a relationship between two individuals i and j by the geometric rate of bilateral e-mail exchange within a window of $\tau = 60$ days (*25*). The instantaneous network at any point in time includes all pairs of individuals that sent one or more messages in each direction during the past 60 days. Using daily network approximations, we calculated (i) shortest path length d_{ij} and (ii) the number of shared affiliations s_{ij} for all pairs of individuals in the network on 210 consecutive days spanning most of the fall and spring semesters (*25*). By identifying new ties that appear in the network over time, we can compute two sets of measures: (i) cyclic closure and (ii) focal closure biases. For some specified value of d_{ij}, cyclic closure bias is defined as the empirical probability that two previously unconnected individuals who are distance d_{ij} apart in the network will initiate a new tie. Thus cyclic closure naturally generalizes the notion of triadic closure (*12*), i.e., formation of cycles of length three. By analogy, we define focal closure bias as the empirical probability that two strangers who share an interaction focus (in the present case, a class) will form a new tie. Because class attendance is relevant mostly for students, the results on focal and cyclic closure are presented here for a subset of 22,611 graduate and undergraduate students (*25*).

Figure 1A (triangles) shows that in the absence of a shared focus (i.e., class), cyclic closure diminishes rapidly in strength with d_{ij}, implying that individuals who are far apart in the network have no opportunity to interact and hence are very unlikely to form ties. For example, individuals who are separated by two intermediaries ($d_{ij} = 3$) are about 30 times less likely to initiate a new tie

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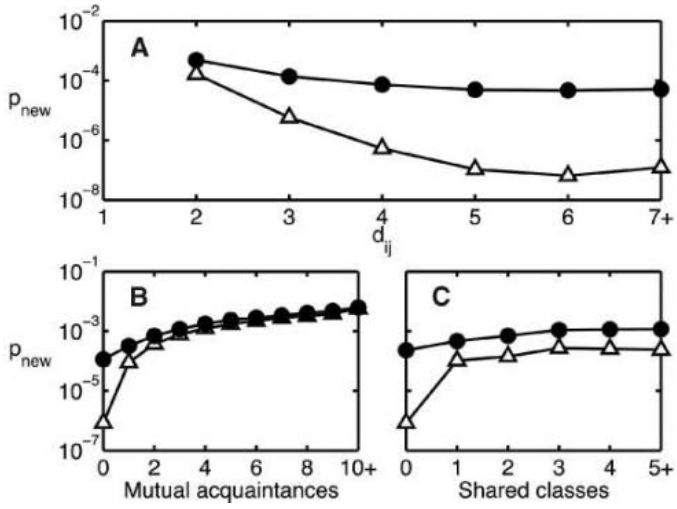

Fig. 1. Cyclic and focal closure. (**A**) Average daily empirical probability p_{new} of a new tie between two individuals as a function of their network distance d_{ij}. Circles, pairs that share one or more interaction foci (attend one or more classes together); triangles, pairs that do not share classes. (**B**) p_{new} as a function of the number of mutual acquaintances. Circles, pairs with one or more shared foci; triangles, pairs without shared foci. (**C**) p_{new} as a function of the number of shared interaction foci. Circles, pairs with one or more mutual acquaintances; triangles, pairs without mutual acquaintances. Lines are shown as a guide for the eye; standard errors are smaller than symbol size.

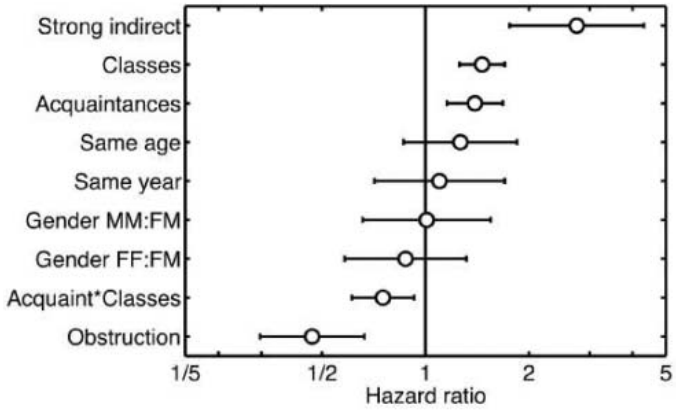

Fig. 2. Results of multivariate survival analysis of triadic closure for a sample of 1190 pairs of graduate and undergraduate students. Shown are the hazard ratios and 95% confidence intervals from Cox regression of time to tie formation between two individuals since their transition to distance $d_{ij} = 2$. Hazard ratio g means that the probability of closure changes by a factor of g with a unit change in the covariate or relative to the reference category. We treat a covariance as significant if the corresponding 95% confidence interval does not contain $g = 1$ (no effect). Predictors, sorted by effect magnitude: strong indirect (1 if indirect connection strength is above sample median, 0 otherwise), classes (number of shared classes), acquaintances (number of mutual network neighbors less 1), same age (1 if absolute difference in age is less than 1 year, 0 otherwise), same year (1 if absolute difference in number of years at the university is less than 1, 0 otherwise), gender [effects of male-male (MM) and female-female (FF) pair, respectively, relative to a female-male (FM) pair], acquaint*classes (interaction effect between acquaintances and classes), and obstruction (1 if no mutual acquaintance has the same status as either member of the pair, 0 otherwise) (*25*).

than individuals who are separated by only one intermediary ($d_{ij} = 2$). Figure 1A (circles), however, demonstrates that when two individuals share at least one class, they are on average 3 times more likely to interact if they also share an acquaintance ($d_{ij} = 2$), and about 140 times more likely if they do not ($d_{ij} > 2$). In addition, Fig. 1B shows that the empirical probability of tie formation increases with the number of mutual acquaintances both for pairs with (circles) and without (triangles) shared classes, becoming independent of shared affiliations for large numbers of mutual acquaintances (six and more). Figure 1C displays equivalent information for shared classes, indicating that while the effect of a single shared class is roughly interchangeable with a single mutual acquaintance, the presence of additional acquaintances has a greater effect than additional foci in our data set. These findings imply that even a minimally accurate, generative network model would need to account separately for (i) triadic closure, (ii) focal closure, and (iii) the compounding effect of both biases together.

Our data can also shed light on theoretical notions of tie strength (*13*) and attribute-based homophily (*6*, *26*). We found (Fig. 2) that the likelihood of triadic closure increases if the average tie strength between two strangers and their mutual acquaintances is high, which supports commonly accepted theory (*6*, *13*). By contrast, homophily with respect to individual attributes appears to play a weaker role than might be expected. Of the attributes we considered in this and other models (*27*)—status (undergraduate, graduate student, faculty, or staff), gender, age, and time in the community—none has a significant effect on triadic closure. The significant predictors are tie strength, number of mutual acquaintances, shared classes, the interaction of shared classes and acquaintances, and status obstruction, which we define as the effect on triadic closure of a mediating individual who has a different status than either of the potential acquaintances. For example, two students connected through a professor are less likely to form a direct tie than two students connected through another student, ceteris paribus. We suspect, however, that status obstruction may be an indicator of unobserved focal closure beyond class attendance. Thus, although homophily has often been observed with respect to individual attributes in cross-sectional data (*6*, *26*), these effects may be mostly indirect, operating through the structural constraint of shared foci (*10*), such as selection of courses or extracurricular activities.

Our results also have implications for the utility of cross-sectional network analysis, which relies on the assumption that the network properties of interest are in equilibrium (*4*). Figure 3 shows that different network measures exhibit varying levels of stability over time and with respect to the smoothing window τ. Average vertex degree $\langle k \rangle$, fractional size of the largest component S, and mean shortest path length L all exhibit seasonal changes and produce different measurements for different choices of τ, where $\langle k \rangle$ is especially sensitive to τ. The clustering coefficient C (*28*), however, stays virtually constant as $\langle k \rangle$ changes, suggesting, perhaps surprisingly, that averages of local network properties are more stable than global properties such as L or S. Nevertheless, these results suggest that as long as the smoothing window τ is chosen appropriately and care is taken to avoid collecting data in the vicinity of exogenous changes (e.g., end of semester), average network measures remain stable over time and thus can be recovered with reasonable fidelity from network snapshots.

The relative stability of average network properties, however, does not imply equivalent stability of individual network properties, for which the empirical picture is more complicated. On the one hand, we find that distributions of individual-level properties are stable, with the same caveats that apply to averages. For example (Fig. 4, A to C), the shape of the degree distribution $p(k)$ is relatively constant across the duration of our

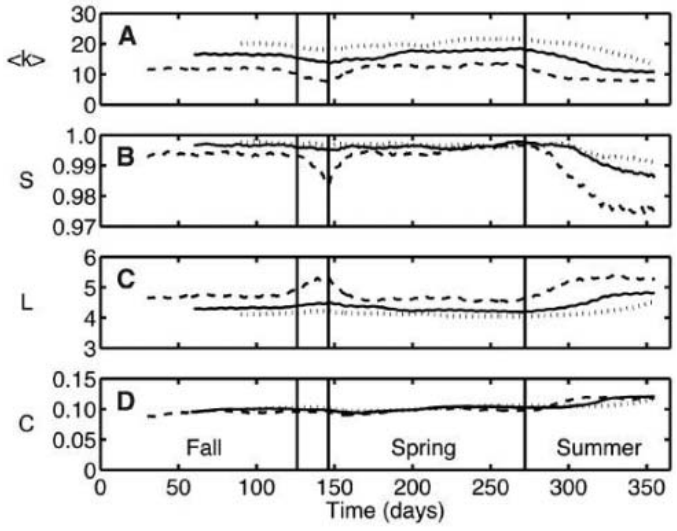

Fig. 3. Network-level properties over time, for three choices of smoothing window τ = 30 days (dashes), 60 days (solid lines), and 90 days (dots). (**A**) Mean vertex degree $\langle k \rangle$. (**B**) Fractional size of the largest component S. (**C**) Mean shortest path length in the largest component L. (**D**) Clustering coefficient C.

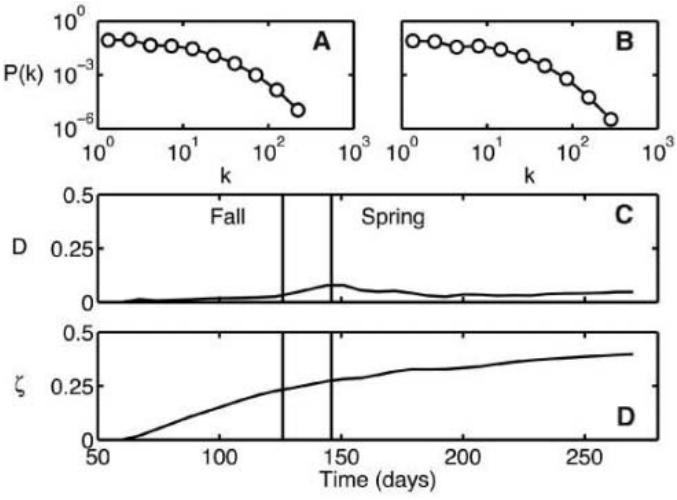

Fig. 4. Stability of degree distribution and individual degree ranks. (**A**) Degree distribution in the instantaneous network at day 61, logarithmically binned. (**B**) Same at day 270. (**C**) The Kolmogorov-Smirnov statistic D comparing degree distribution in the instantaneous network at day 61 and in subsequent daily approximations. (**D**) Dissimilarity coefficient for degree ranks $\zeta = 1 - r_S^2$, where r_S is the Spearman rank correlation between individual degrees at day 61 and in subsequent approximations. ζ varies between 0 and 1 and measures the proportion of variance in degree ranks that cannot be predicted from the ranks in the initial network.

data set except during natural spells of reduced activity, such as winter break (Fig. 4C). On the other hand, as Fig. 4D illustrates, individual ranks change substantially over the duration of the data set. Analogous results (*27*) apply to the concept of "weak ties" (*13*): The distribution of tie strength in the network is stable over time, and bridges are, on average, weaker than embedded ties [consistent with (*13*)]. However, they do not retain their bridging function, or even remain weak, indefinitely.

Our results suggest that conclusions relating differences in outcome measures such as status or performance to differences in individual network position (*14*) should be treated with caution. Bridges, for example, may indeed facilitate diffusion of information across entire communities (*13*). However, their unstable nature suggests that they are not "owned" by particular individuals indefinitely; thus, whatever advantages they confer are also temporary. Furthermore, it is unclear to what extent individuals are capable of strategically manipulating their positions in a large network, even if that is their intention (*14*). Rather, it appears that individual-level decisions tend to "average out," yielding regularities that are simple functions of physical and social proximity. Sharing focal activities (*10*) and peers (*26*), for example, greatly increases the likelihood of individuals becoming connected, especially when these conditions apply simultaneously.

It may be the case, of course, that the individuals in our population—mostly students and faculty—do not strategically manipulate their networks because they do not need to, not because it is impossible. Thus, our conclusions regarding the relation between local and global network dynamics may be specific to the particular environment that we have studied. Comparative studies of corporate or military networks could help illuminate which features of network evolution are generic and which are specific to the cultural, organizational, and institutional context in question. We note that the methods we introduced here are generic and may be applied easily to a variety of other settings. We conclude by emphasizing that understanding tie formation and related processes in social networks requires longitudinal data on both social interactions and shared affiliations (*4*, *6*, *10*). With the appropriate data sets, theoretical conjectures can be tested directly, and conclusions previously based on cross-sectional data can be validated or qualified appropriately.

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Integration of Plant Responses to Environmentally Activated Phytohormonal Signals

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Plants live in fixed locations and survive adversity by integrating growth responses to diverse environmental signals. Here, we show that the nuclear-localized growth-repressing DELLA proteins of *Arabidopsis* integrate responses to independent hormonal and environmental signals of adverse conditions. The growth restraint conferred by DELLA proteins is beneficial and promotes survival. We propose that DELLAs permit flexible and appropriate modulation of plant growth in response to changes in natural environments.

Plants integrate multiple environmental signals during growth regulation. We determined whether the DELLA proteins specifically restrain growth in adverse conditions. DELLAs are nuclear proteins that restrain the cell proliferation and expansion that drives plant growth (*1*–*3*). The phytohormone gibberellin (GA) stimulates growth by promoting the destruction of DELLAs (*4*, *5*), and the phytohormones auxin and ethylene also regulate DELLA restraint (*6*–*8*).

High salinity restricts root water uptake, damages cell physiology, and slows growth (*9*, *10*). We found that the growth of *Arabidopsis* "quadruple-DELLA mutant" seedlings lacking GAI, RGA, RGL1, and RGL2 [four of the five DELLAs encoded by the *Arabidopsis* genome (*11*)] was less inhibited by salt than that of the wild type (Fig. 1, A to D). For example, root elongation of quadruple-DELLA mutants was relatively resistant to salt (Fig. 1B), although not completely resistant (perhaps because RGL3 remains in the quadruple-DELLA mutant line, or as a result of DELLA-independent mechanisms). In addition, salt slowed the leaf production rate (Fig. 1C), leaf expansion (*12*), and biomass accumulation (Fig. 1D) of wild-type plants but had a reduced effect on that of quadruple-DELLA mutants. Finally, we found that salt-treated wild-type plants contained reduced levels of bioactive GAs (GA_1 and GA_4; Fig. 1D). Thus, salt slows growth by means of a DELLA-dependent mechanism that is associated with reduced accumulation of bioactive GAs.

Reduced GA accumulation causes increased accumulation of DELLAs (*13*, *14*) and consequent growth inhibition. We found that DELLA-dependent salt-induced growth inhibition is also associated with DELLA accumulation. A green fluorescent protein–tagged DELLA (GFP-RGA) accumulated to higher levels in salt-treated *pRGA:GFP-RGA* roots (*6*, *7*, *14*) than in controls (Fig. 1E), despite lack of detectable effect on the levels of *RGA* transcripts (fig. S1). Because GA treatment caused a reduction in GFP-RGA levels in nuclei of salt-treated roots (Fig. 1E), it is likely that salt stress [and other kinds of stress (*15*)] inhibits growth by means of the above identified reduction in bioactive GA level, with consequent accumulation of DELLAs.

Plant salt responses are triggered (at least in part) by increased levels of the phytohormone abscisic acid (ABA) and resultant activation of ABA signaling pathways (*9*, *16*). Indeed, *abi1-1* mutant roots [in which a mutant form of the ABI1 serine/threonine protein phosphatase confers reduced ABA signaling (*17*, *18*)] were resistant to the growth-inhibitory effects of both ABA and salt (Fig. 1B) (*17*), indicating that ABI1-dependent ABA signaling is necessary for normal levels of salt-induced root growth inhibition. Furthermore, GFP-RGA accumulated in ABA-treated roots (Fig. 1F) but not in ABA-treated *abi1-1* roots (fig. S2), whereas quadruple-DELLA mutant roots were relatively resistant to the growth-inhibitory effects of ABA (Fig. 1B). These results suggest that salt inhibits growth (at least in part) by means of ABI1-dependent ABA-mediated enhancement of DELLA restraint.

Exposure to high salinity induces rapid increases in the level of "stress-induced" gene transcripts by means of ABA-dependent and -independent signaling pathways (*16*). However, we found no evidence that DELLAs are involved in the salt inducibility of selected stress-inducible transcripts (fig. S3). Thus, DELLAs regulate the plant "growth response" to salt but do not regulate the levels of the salt-induced transcripts tested here.

The plant life-cycle consists of successive embryonic, vegetative, and reproductive (flowering) developmental phases (*19*). DELLAs delay flowering, particularly in short-day (SD) photoperiods (*20*). Exposure of wild-type plants to salt (*21*) delayed flowering (*10*) (Fig. 2A), irrespective of whether flowering was measured as days to flowering (Fig. 2B), or as number of leaves in the vegetative rosette at bolting (Fig. 2C). In contrast, salt-treated quadruple-DELLA mutants flowered earlier than wild-type controls (Fig. 2, A to C). Thus, salt extends the duration of the vegetative phase by means of a DELLA-dependent mechanism. Furthermore, the extreme effect of salt on the growth rates of the GA-deficient *ga1-3* mutant (*12*) and on the *gai* mutant [which contains a mutant DELLA that is relatively resistant to the effects of GA (*2*, *5*)] prevented flowering within the duration of the experiment (fig. S4).

Flowering is induced by changes in the abundance of transcripts encoding proteins that have floral-promotive or floral-inhibitory function (*19*). For example, *FLOWERING LOCUS C* (*FLC*) transcripts repress flowering, whereas *SUPPRESSOR OF OVEREXPRESSION OF CONSTANS* (*SOC1*), *FLOWERING LOCUS T* (*FT*), *CONSTANS* (*CO*), and *LEAFY* (*LFY*) transcripts promote flowering (*1*, *19*, *20*, *22*–*24*). We found that *CO* transcript levels were slightly reduced, *FLC* transcript levels were slightly increased, and *SOC1* and *FT* transcript levels were not detectably affected in plants grown on salt (Fig. 2D). Furthermore, the relatively rapid flowering of the quadruple-DELLA mutant on salt occurred independently of any detectable effect of DELLAs on the levels of *FLC*, *SOC1*, *FT*, or *CO* transcripts (Fig. 2D). In contrast, *LFY* transcripts were at a substantially reduced level in salt-treated wild-type plants (versus controls) but in salt-treated quadruple-DELLA mutants were at a similar level to those in wild-type controls (Fig. 2D). These observations suggest that salt delays flowering by means of two distinct mechanisms. First, salt slows growth by means of DELLA restraint, thus increasing the duration of the vegetative phase. Second, salt acts by means of DELLAs to inhibit flowering by maintaining relatively low levels of *LFY* transcript. It is possible that *LFY*-dependent regulation of flowering (by means of the GA-DELLA pathway) has increased importance (compared with other floral promotive pathways) in salt-treated plants, as it does in SD (*20*, *22*–*24*). Lastly, we found that ABA delays flowering in a DELLA-dependent manner, again affecting both days to flowering and leaf rosette number (fig. S5). This suggests that salt delays flowering through the same mechanism that contributes to inhibition of vegetative growth (Fig. 1B), by means of ABA-dependent enhancement of DELLA restraint (Fig. 1F).

Ethylene is another phytohormone that signals adverse environments. For example, adversity causes rapid increases in the activity of

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1-aminocyclopropane-1-carboxylic acid (AAC) synthase (ACS), a rate-limiting step in ethylene production (*25*). We found that salt caused an increase in the seedling levels of ACS-encoding *ACS2* and *ACS7* transcripts (*25*) (Fig. 3A), an increase in detectable levels of emanated ethylene (Fig. 3B), and an increase in the levels of ethylene-inducible *CHI-B* and *ERF4* transcripts (*26*, *27*) (Fig. 3A). None of the above ethylene-related salt responses were detectably altered in *gai* or *ga1-3*, in mutants lacking GAI and RGA (*gai-t6 rga-24*), or in the quadruple-DELLA mutant (Fig. 3, A and B). Growth of plants in an ethylene-enriched atmosphere delayed wild-type flowering but was less inhibitory of the flowering of both *gai-t6 rga-24* and quadruple-DELLA mutant plants (Fig. 3C). Thus, salt extends the duration of the vegetative phase through activation of both ABA and ethylene signaling, two independent pathways whose effects are integrated at the level of DELLA function.

Extreme salt concentrations kill plants (*15*), and we found that DELLAs determine the survival of salt toxicity. For example, the *ga1-3* and *gai* mutations conferred increased tolerance of a salt concentration that kills a proportion (~35%) of wild-type plants (*15*) (Fig. 4 and fig. S6), suggesting that stabilized DELLAs enhance survival in saline environments. Furthermore, lack of GAI, RGA, RGL1, and RGL2 suppressed the salt tolerance conferred by *ga1-3* (Fig. 4B), whereas the quadruple-DELLA mutant was less salt tolerant than the wild type (Fig. 4 and fig. S6). Thus, DELLA function promotes salt tolerance. Indeed, as salt concentrations increase, the growth of quadruple-DELLA mutant roots becomes more inhibited than that of the wild type, presumably due to the increased damage susceptibility that reduced DELLA function confers (fig. S7).

We next found that ethylene signaling promotes salt tolerance in a DELLA-dependent fashion. Wild-type plants treated with the ethylene precursor ACC (*25*) displayed increased tolerance of high-salt environments (*12*). In the absence of ethylene, degradation of the EIN3 transcription factor is promoted by the E3 ubiquitin ligase $SCF^{EBF1/EBF2}$ (*28*–*30*). Mutant plants lacking $SCF^{EBF1/EBF2}$ (*ebf1-1 ebf2-1*), or lacking the upstream CTR1 Ser/Thr kinase (*ctr1-1*), exhibit constitutive ethylene responses due to EIN3 accumulation (*28*–*30*). We found that *ein3-1* mutants (lacking EIN3) exhibited reduced salt tolerance and that *ctr1-1* and *ebf1-1 ebf2-1* mutants exhibited increased salt tolerance (Fig. 4, A and B). The increased salt tolerance of *ebf1-1 ebf2-1* mutants was abolished by lack of EIN3 (in *ein3-1 ebf1-1 ebf2-1* mutant plants; Fig. 4). Furthermore, lack of GAI and RGA (in *ctr1-1 gai-t6 rga-24*) substantially suppressed the salt tolerance exhibited by *ctr1-1* (Fig. 4), thus demonstrating that EIN3 promotes salt tolerance by enhancing DELLA function. In addition, we found that the *abi1-1* mutation

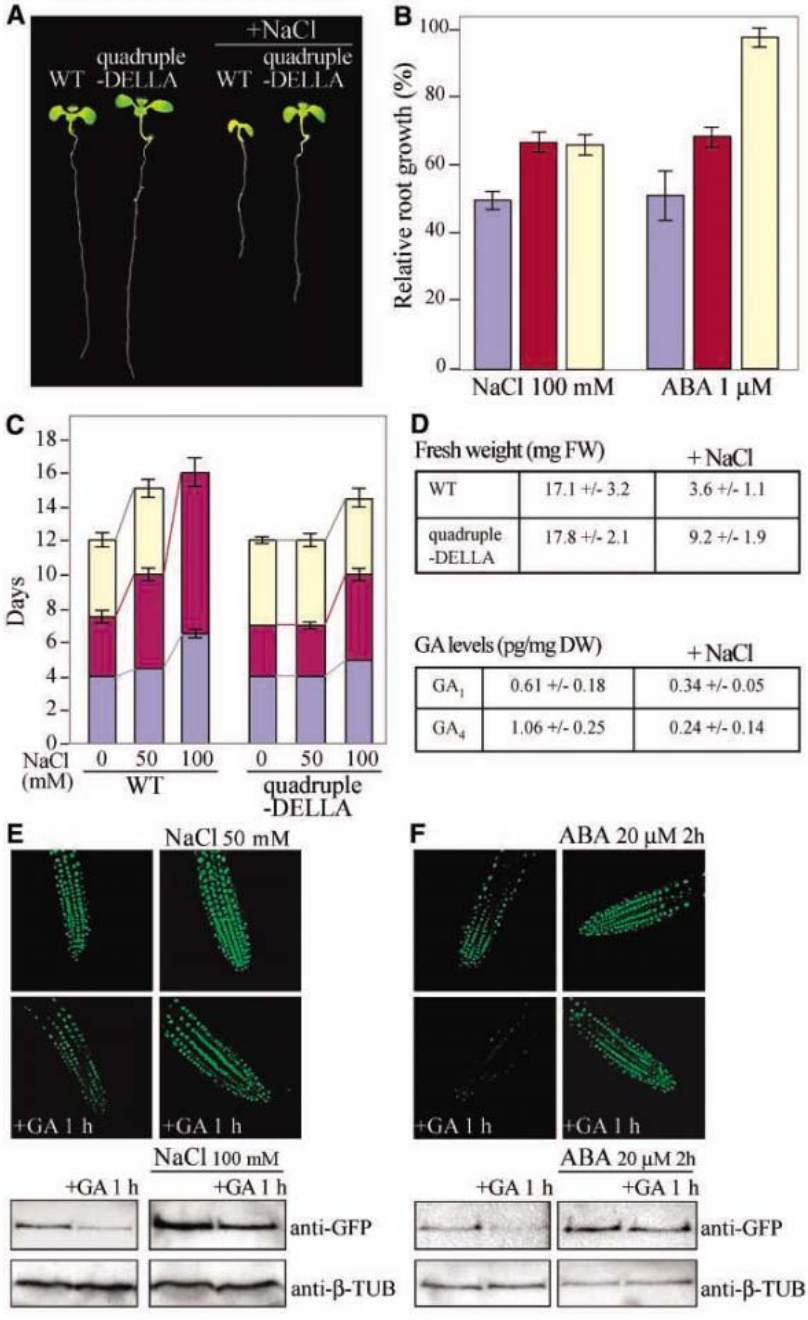

Fig. 1. Salt slows vegetative growth by enhancing DELLA function. (**A**) Representative 7-day-old wild-type and quadruple-DELLA mutant (*gai-t6 rga-t2 rgl1-1 rgl2-1*) seedlings grown on 100 mM NaCl (and controls). (**B**) Mean (±SE) relative growth of primary roots of 7-day-old wild-type (blue), quadruple-DELLA mutant (red), and *abi1-1* (yellow) seedlings grown in the presence of 100 mM NaCl or 1 μM ABA (expressed as percentage of untreated control). (**C**) Mean (±SE) rate of production of leaves by wild-type and quadruple-DELLA mutant vegetative rosettes grown on 0, 50, or 100 mM NaCl. Colors show the period until appearance of first (blue), second (red), and third (yellow) pair of rosette (true) leaves. (**D**) Mean fresh weights (FW) (±SE) of 14-day-old wild-type and quadruple-DELLA plants grown on 100 mM NaCl (+NaCl) and control; mean GA levels [picograms per milligram dry weight (DW); ±SD; $n = 4$] in 14-day-old wild-type seedlings grown on 100 mM NaCl (+NaCl) and control. (**E**) GFP fluorescence (viewed by fluorescence confocal microscopy) in tips of *pRGA:GFP-RGA* primary seedling roots after a 1-hour treatment with 10 μM GA_3 (+GA) (or control) in the presence or absence of NaCl, together with immunodetected (by an antibody to GFP) GFP-RGA in salt-treated (or control) GA-treated (or control) *pRGA:GFP-RGA* roots. β-tubulin (β-TUB) serves as a sample-loading control. (**F**) Same as (E) except that ABA (concentration as shown) was used in place of NaCl.

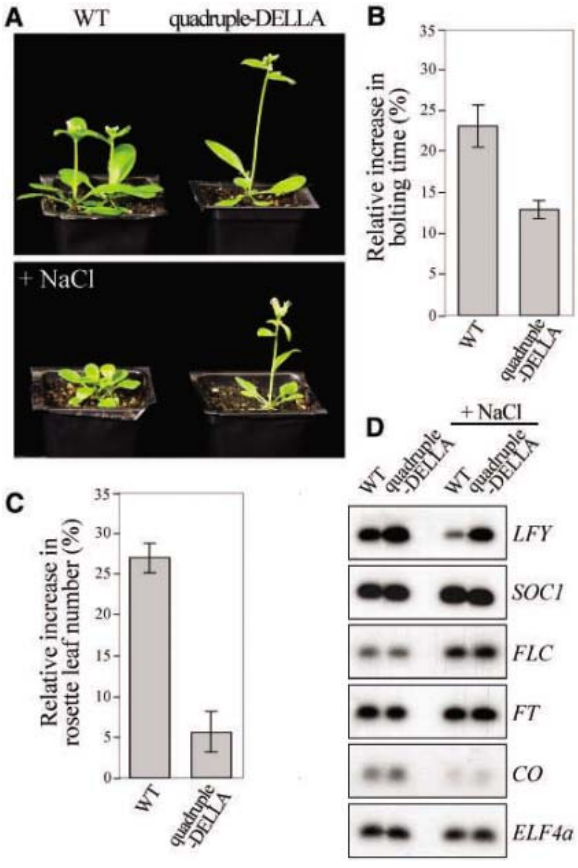

Fig. 2. Salt extends the vegetative phase of the life cycle through a DELLA-dependent mechanism. (**A**) Representative (30-day-old) wild type (two plants are shown) and quadruple-DELLA mutants (single plants) grown on soil and watered with saline solution [200 mM NaCl (+NaCl)] or control. (**B** and **C**) Mean (±SE) relative increase in bolting time (B) and number of rosette leaves (C) of wild-type and quadruple-DELLA mutant plants grown on soil and watered with saline solution (200 mM NaCl), expressed as a percentage of the untreated control. (**D**) Levels of floral integrator gene transcripts [determined by reverse transcription polymerase chain reaction (RT-PCR)] in soil-grown NaCl-treated wild-type and quadruple-DELLA mutant plants (and controls). *ELF4a* transcripts provide loading control.

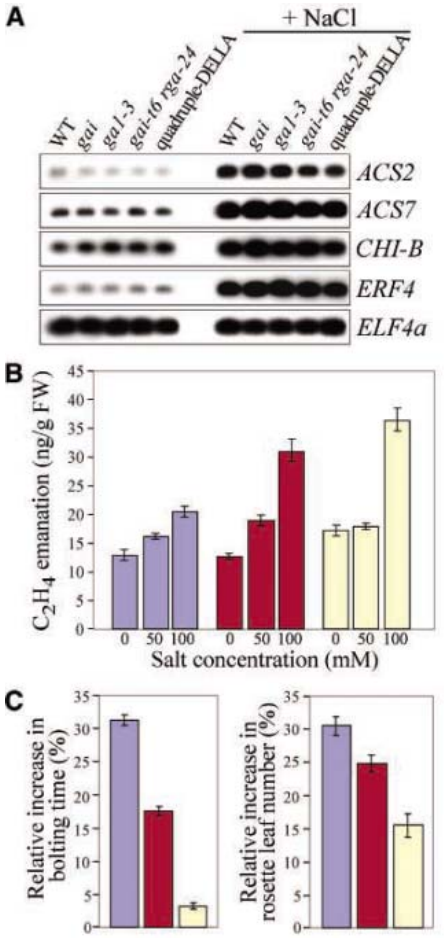

Fig. 3. Salt delays flowering by means of a DELLA-dependent ethylene response. (**A**) Levels of selected ethylene biosynthesis and ethylene-responsive gene transcripts (determined by RT-PCR) in 14-day-old plants of the wild type and various genotypes (as indicated) treated with 200 mM NaCl (and controls). *ELF4a* transcripts provide loading control. (**B**) Ethylene gas emanation [nanograms ethylene per gram fresh weight (FW); ±SE; $n = 4$] of 3-week-old wild-type (blue), *gai-t6 rga-24* (red), and quadruple-DELLA mutant (yellow) plants treated with increasing concentrations of NaCl. (**C**) Mean (±SE) relative increase in bolting time and rosette leaf number of wild-type (blue), *gai-t6 rga-24* (red), and quadruple-DELLA mutant (yellow) plants grown in an ethylene-enriched atmosphere (1 part per million), expressed as in Fig. 2, B and C.

conferred reduced salt tolerance (Fig. 4B). This observation, together with our previous ABA-related results, suggests that salt-activated ethylene and ABA signaling pathways integrate at the level of DELLA function to promote salt tolerance.

Although it was previously clear that environmental regulation of plant growth and developmental progression required signal integration, the nature of this integration was unknown. Here, we show that two independent salt-activated phytohormonal signaling pathways (ABA and ethylene) regulate plant development through integration at the level of DELLA function. Because the ABA and ethylene pathways are involved in plant responses to diverse abiotic and biotic inputs, it is likely that DELLA restraint provides a general mechanism for integration of plant growth responses to the environment.

Our results also identify a previously unknown mechanism that permits plant growth response to adversity. Salt-activated signaling pathways enhance the growth-repressing effects of DELLAs, at least in part through a reduction in the levels of bioactive GAs. The resultant accumulation of DELLAs then slows the rate of growth and extends the duration of the vegetative growth phase. This enhanced growth repression is distinct from passive growth rate reductions due to salt-induced perturbation of the physiological and metabolic processes that drive growth. Genetic analysis indicates that of the four *Arabidopsis* DELLA proteins, it is the combined effects of GAI and RGA that predominate in salt-activated growth repression (supporting online material text and fig. S8), the two DELLAs known to play the major role in DELLA-mediated plant growth regulation (*13*).

We show that DELLA-dependent growth restraint is advantageous in adverse environments. Perhaps growth restraint enables the redirection of resources to support mechanisms that promote survival of adversity. Alternatively, smaller plants may be less vulnerable to stress because they have less surface area. Although the nature of these underlying mechanisms remains unknown, it is nevertheless clear that DELLA restraint permits a flexible growth response to environmental variability, thus promoting survival.

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B

Lines	Total plants	Survival	Rate (%)
Ler	44	16	36.4
ga1-3	44	41	93.2
gai	44	36	81.8
gai-t6 rga-24	44	2	4.5
gai-t6 rga-t2 rgl1-1 rgl2-1	44	3	6.8
ga1-3 gai-t6 rga-24	40	2	5
ga1-3 gai-t6 rga-t2 rgl1-1 rgl2-1	40	2	5
abi1-1	30	6	20
Col	40	14	35
ctr1-1	40	36	90
ein3-1	40	8	20
ebf1-1 ebf2-1	40	35	87.5
ebf1-1 ebf2-1 ein3-1	32	5	15.6
ctr1-1 3xBC Ler	30	29	96.6
ctr1-1 gai-t6 rga-24	30	16	53.3

Fig. 4. DELLA-dependent survival of toxic salt concentrations. (**A**) Survival of representative plants of various genotypes (as indicated) on high-salt medium (200 mM). Photograph taken 10 days after transfer of plants to high-salt medium. Live plants are green; dead plants are white. (**B**) Numbers of plants of various genotypes [expressed as number of surviving plants and rate of survival (%)] that survive growth on high-salt medium.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/311/5757/91/DC1
Materials and Methods
SOM Text
Figs. S1 to S8
References

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Cytokinin Signaling and Its Inhibitor AHP6 Regulate Cell Fate During Vascular Development

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The cell lineages that form the transporting tissues (xylem and phloem) and the intervening pluripotent procambial tissue originate from stem cells near the root tip. We demonstrate that in *Arabidopsis*, cytokinin phytohormones negatively regulate protoxylem specification. AHP6, an inhibitory pseudophosphotransfer protein, counteracts cytokinin signaling, allowing protoxylem formation. Conversely, cytokinin signaling negatively regulates the spatial domain of *AHP6* expression. Thus, by controlling the identity of cell lineages, the reciprocal interaction of cytokinin signaling and its spatially specific modulator regulates proliferation and differentiation of cell lineages during vascular development, demonstrating a previously unrecognized regulatory circuit underlying meristem organization.

The root vascular cylinder has a central axis of xylem cell files consisting of protoxylem at marginal positions and metaxylem at central positions. This axis is flanked by phloem and intervening procambial cell files. A proportion of these intervening procambial cell files becomes mitotically active during secondary development and forms the lateral meristem, cambium, through periclinal divisions (*1*, *2*) (Fig. 1A). Cytokinins have been implicated in controlling vascular morphogenesis (*2*–*5*). The *wooden leg* (*wol*) allele of *CRE1* and the triple-knockout mutant for all three genes encoding CRE-family receptors (CRE1/WOL/AHK4, AHK2, and AHK3) display a markedly reduced number of cell files within the vascular bundle, because the periclinal procambial cell divisions required to proliferate the vascular cell files do not occur. This is associated with specification of all the vascular cell files in the root as protoxylem (*2*, *6*, *7*) (fig. S3B). This phenotype can be copied through depleting cytokinins by expressing the *CYTOKININ OXIDASE 2* gene (*8*) under the control of the procambium-specific *CRE1* promoter (fig. S3B), indicating that cytokinin signaling through the CRE-family receptors is required for proliferation and/or maintenance of the procambium.

To investigate whether reduced cell number is a prerequisite for exclusive protoxylem differentiation, we depleted cytokinins postembryonically by expressing cytokinin oxidase 1–yellow fluorescent protein (YFP) under the

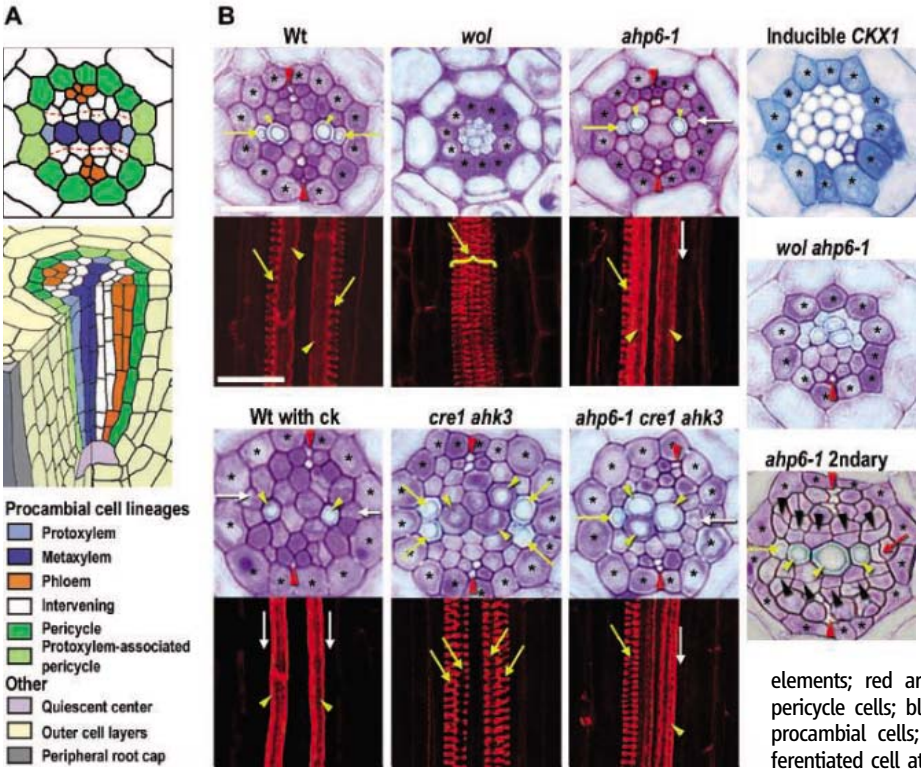

Fig. 1. Cytokinin signaling inhibits protoxylem differentiation. (**A**) Schematic of *Arabidopsis* root vasculature from a mature (transverse section, top) and meristematic procambial regions (three-dimensional representation, bottom). The pattern of periclinal cell divisions of the intervening procambial tissue characteristic to secondary development is shown with dotted red lines. (**B**) Histological analysis of root vasculature stained with toluidine blue (top) and fuchsin red (bottom, where provided) indicates that protoxylem is more abundant in genetic backgrounds with reduced cytokinin signaling, and *ahp6* is able to suppress *wol* and *cre1 ahk3*. Fuchsin staining highlights lignified regions; the helical staining pattern is characteristic of protoxylem, whereas the pitted or reticulate pattern is characteristic of metaxylem. Inducible *CKX1* indicates that *CKX1-YFP* was induced postgermination in a tissue-specific manner with the use of *CRE1prom::XVE/LexAoperator::CKX1-YFP* in wild-type roots; Wt with CK, wild-type seedling germinated with 100 nM benzyladenine (a cytokinin); 2ndary, during secondary development. Yellow arrows, protoxylem elements; white arrows, absence of protoxylem; yellow arrowheads, metaxylem elements; red arrowheads, sieve elements of protophloem; asterisks, pericycle cells; black arrowheads, periclinal cell division in intervening procambial cells; and red arrow, periclinal cell division of an undifferentiated cell at the protoxylem position. Scale bar, 20 μm.

CRE1 promoter, in an estrogen-inducible fashion (*8*, *9*). After induction, all cell files within the root vascular cylinder differentiated as protoxylem (Fig. 1B and fig. S1). Furthermore, when wild-type seedlings were grown on media containing cytokinin, protoxylem differentiation and green fluorescent protein (GFP) expression of the enhancer trap line J0121, which highlights the protoxylem-associated pericycle cells (*10*), were severely impaired or even eliminated (Figs. 1B and 2E and figs. S2 and S4B). Together, these results indicate that cytokinin signaling is required to promote and maintain cell identities other than protoxylem, and in the absence of cytokinin signaling, protoxylem is the "default" identity.

To identify molecules regulating cytokinin-mediated vascular morphogenesis, we performed a suppressor screen for the determinate root growth associated with *wol* (*6*). Two allelic, recessive, extragenic suppressor mutations were identified, *ahp6-1* and *ahp6-2* (Fig. 2A). Compared with *wol*, *wol ahp6* roots display an increased number of vascular cell files with intervening procambial and phloem cell files present (Fig. 1B and fig. S3, A and C). Neither *ahp6-1* nor *ahp6-2* plants display an obvious seedling phenotype. However, histological studies revealed that protoxylem differentiation occurred sporadically along the root (Fig. 1B and figs. S3D and S4). Quantitative analysis showed that this phenotype is less prominent in *ahp6-2*, indicating that *ahp6-1* is a stronger allele (fig. S4B). Expression of a molecular marker highlighting immature xylem cells (*ZCP4prom::GUS*) (*11*) coincides with visible xylem differentiation in wild-type and *ahp6-1* roots (Fig. 2D). Furthermore, expression of the *GFP* transcript in the enhancer trap line J0121 (*10*) is slightly down-regulated in *ahp6-1* roots (Fig. 2E) (*12*). To further investigate cell fate at the protoxylem position in *ahp6-1* roots, we analyzed the vascular pattern during secondary development when the intervening procambial cell files undergo periclinal cell divisions in wild-type and *ahp6-1* roots (Fig. 1A). Notably, these cells underwent periclinal divisions simultaneously with the neighboring procambial cells files (Fig. 1B and fig. S5). In wild-type roots, this position is invariably differentiated as protoxylem (fig. S4B). In conclusion, the *ahp6* phenotypes in *wol* and in wild-type roots reveal a role for the *AHP6* locus in promoting the specification of protoxylem.

To characterize the *AHP6* locus at the molecular level, we determined through positional cloning that both *ahp6-1* and *ahp6-2* contain mutations in the gene *ARABIDOPSIS HISTIDINE PHOSPHOTRANSFER PROTEIN 6* (*AHP6*), At1g80100 in the *Arabidopsis* Genome Initiative database (Fig. 3A). A genomic DNA fragment containing the *AHP6* locus complemented *ahp6-1* (Fig. 2A and fig. S3C). Current evidence supports a model of signal transduction in which cytokinins first activate phosphotransfer from adenosine 5′-triphosphate (ATP) to the three CRE-family receptors, and then the phosphoryl group is transferred to the conserved histidine residue of the AHP proteins (AHP1 to AHP5) and finally to response regulators governing physiological responses (*13*, *14*). AHP6 lacks the conserved histidine residue (fig. S6) (Asn^{83} in AHP6b), which is required for phosphotransfer and is present in the other AHPs (*13*, *15*). We identified cDNA for two independent transcripts (*AHP6a*-DQ093642 and *AHP6b*-DQ093643), differing in the length of the first exon (Fig. 3, A and B). The mutation in *ahp6-1* resulted in a premature stop codon in the first exon (CAG to TAG, at Gln^{35}), and the mutation in *ahp6-2* (G to A) was located in the first intron, 5 base pairs from the 5′ border of the *AHP6b* splice variant. In *ahp6-2* seedlings, only the *AHP6a* transcript is present (Fig. 3B). Given that this represents a weak allele, it is likely that both transcripts are functional. We also identified a transferred DNA (T-DNA) insertion allele (at Ser^{111} of AHP6b), *ahp6-3*, which phenocopies *ahp6-1* (Fig. 3A and figs. S3D and S4B). Because the open reading frame is terminated early in *ahp6-1*, and because only

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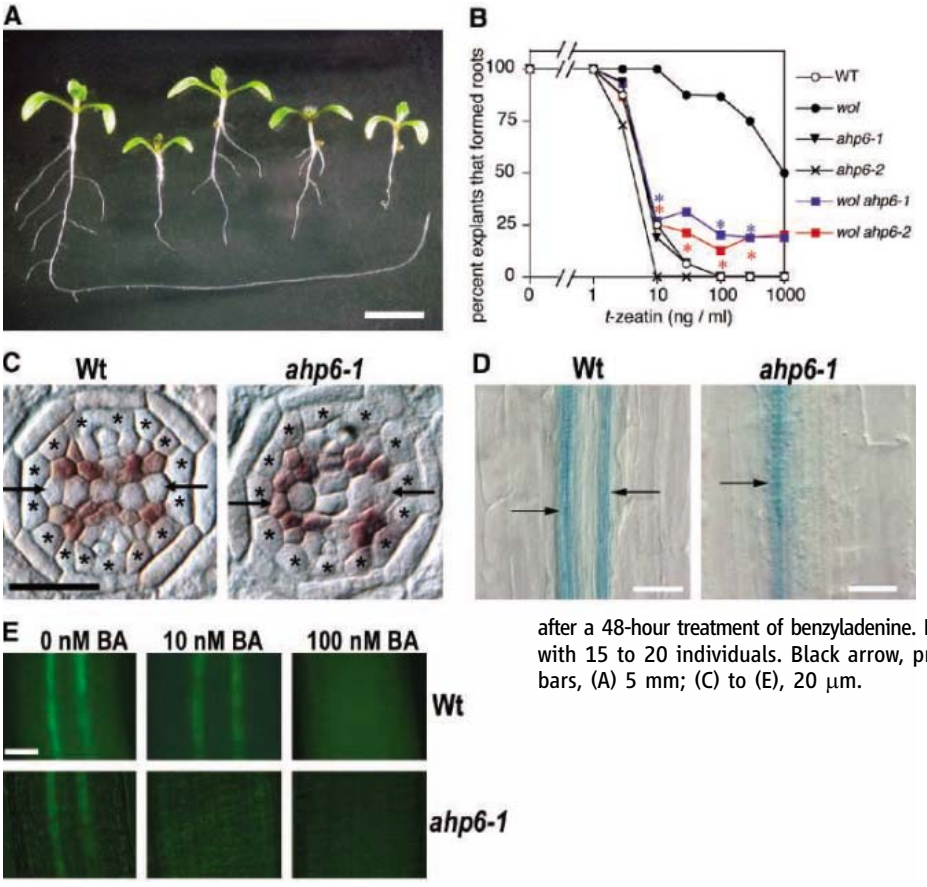

Fig. 2. Phenotypic analysis of *ahp6* mutants. (**A**) From left to right: wild type, *wol*, *wol ahp6-1*, *wol ahp6-2*, and *wol ahp6-1* complemented with *AHP6prom::AHP6*. (**B**) The adventitious root formation assay indicates that *ahp6* mutants confer increased cytokinin responsiveness in *wol* background. Cytokinins normally inhibit the formation of adventitious roots near the cut end of a hypocotyl. The percent of explants producing adventitious roots when grown on media with increasing concentrations of *t*-zeatin (a cytokinin) is presented. Significant differences existed between *wol* and *wol ahp6-1* (blue asterisk) or between *wol* and *wol ahp6-2* (red asterisk), according to the Fisher's exact probability test ($P < 0.05$). (**C**) In situ hybridization with an antisense probe reveals *ARR15* expression at the protoxylem position in *ahp6-1*. A sense probe showed no detectable signal (*12*). (**D**) Loss of protoxylem differentiation is accompanied with loss of *ZCP4prom::GUS* expression in *ahp6-1*. (**E**) Expression of J0121, a GFP marker line with expression specifically in protoxylem-associated pericycle cells (Fig. 1A and fig. S2) is down-regulated after a 48-hour treatment of benzyladenine. Panels shown are representative of analyses performed with 15 to 20 individuals. Black arrow, protoxylem position; asterisks, pericycle cells. Scale bars, (A) 5 mm; (C) to (E), 20 μm.

reduced level of *AHP6* message was detected upstream and no message was detected downstream of the T-DNA insertion in *ahp6-3*, these are likely to represent null alleles (Fig. 3B).

To investigate the biochemical nature of AHP6 function, we based an in vitro assay around the already well-characterized phosphotransfer activity of the yeast SLN1 histidine kinase (*16*). The histidine kinase domain (SLN1HisK) and the receiver domain (SLN1Rec) were prepared as separate peptides, enabling examination of interdomain phosphotransfer (*16*). In this assay, the phosphoryl group is transferred from ^{32}P-labeled ATP to a conserved His residue of SLN1HisK, then to a conserved Asp residue within the SLN1Rec, and subsequently to a conserved His residue within an HPt protein. Using this in vitro phosphotransfer system, we demonstrated that AHP1 to AHP3, AHP5, and a mutant version of AHP6b (Asn^{83} replaced with the conserved His required for phosphotransfer activity) were able to accept a phosphoryl group from SLN1 (Fig. 3C and fig. S7). In contrast, native AHP6 was unable to accept a phosphoryl group. These results suggest that AHP6 does not function as a phosphotransfer protein. Although AHP6 does not appear to have phosphotransfer activity, it was able to inhibit phosphotransfer from the SLN1HisK to SLN1Rec. We also examined the effect of AHP6 on phosphotransfer from AHP1 to an *Arabidopsis* response regulator, ARR1 (Fig. 3C). When phosphorylated AHP1 and ARR1 were co-incubated, phosphotransfer occurred from phosphorylated AHP1 to ARR1, and this was inhibited by AHP6 (Fig. 3C). Taken together, the evidence suggests that AHP6 acts as an inhibitor of cytokinin signaling by interacting with the phosphorelay machinery, potentially at multiple steps. Database searches using the AHP6 sequence reveal homologs in other plant species (fig. S6), indicating that the negative regulation of the His-to-Asp phosphorelay system by pseudo-HPts may be widespread in the plant kingdom.

Using in situ RNA hybridization, and the *AHP6prom::GUS* and *AHP6prom::GFP* reporter constructs, we observed expression of *AHP6* in developing protoxylem and associated pericycle cell files, revealing a spatially specific expression pattern consistent with the mutant phenotype (Figs. 3, D and E, and 4A; fig. S8A). GFP signal is ubiquitous in the cotyledons of heart-shaped embryos and is gradually restricted to two poles by the late heart stage/early torpedo stage of embryogenesis (Fig. 3F and fig. S8C). By the mature stage, GFP expression is refined to the cotyledon apices and two poles in the embryonic root which later form protoxylem. *AHP6* is also expressed in the shoot apex and young leaves (fig. S8A). The existence of the AHP6 protein was confirmed by complementing *ahp6-1* with *AHP6prom::AHP6-GFP* and observing GFP signal (fig. S8B).

To examine the role of AHP6 in cytokinin signaling, cytokinin responsiveness conferred by *ahp6* was measured with the use of the adventitious root formation assay (*17*). The impaired cytokinin response in *wol* was partially restored in *wol ahp6* (Fig. 2B, consistent with the negative role of AHP6 on cytokinin signaling. We also demonstrated that *ahp6-1* could not suppress the cytokinin-insensitive *cre1 ahk2 ahk3* phenotype, indicating that the suppressor phenotype in the *wol* background is due to residual cytokinin signaling (*17*) (Fig. 2B and fig. S3C). To study the status of cytokinin signaling in *ahp6-1* at the position normally occupied by protoxylem files, we performed in situ RNA hybridization, with the cytokinin primary response gene *ARR15* (*18*) as a probe (Fig. 2C). Whereas *ARR15* expression in wild-type roots was restricted to the intervening procambial cells adjacent to the xylem axis ($n = 4$), the expression domain in four out of five *ahp6-1* roots expanded to include the protoxylem position. These results indicate that AHP6 functions to facilitate protoxylem specification by down-regulating cytokinin signaling in a spatially specific manner. To confirm this, we examined whether the cytokinin-degrading enzyme CKX2 (*8*) could substitute AHP6 when ectopically expressed in the protoxylem. *AHP6prom::CKX2* suppressed the *ahp6-1* phenotype (fig. S3D). Furthermore, when *ahp6-1* plants were germinated on media containing

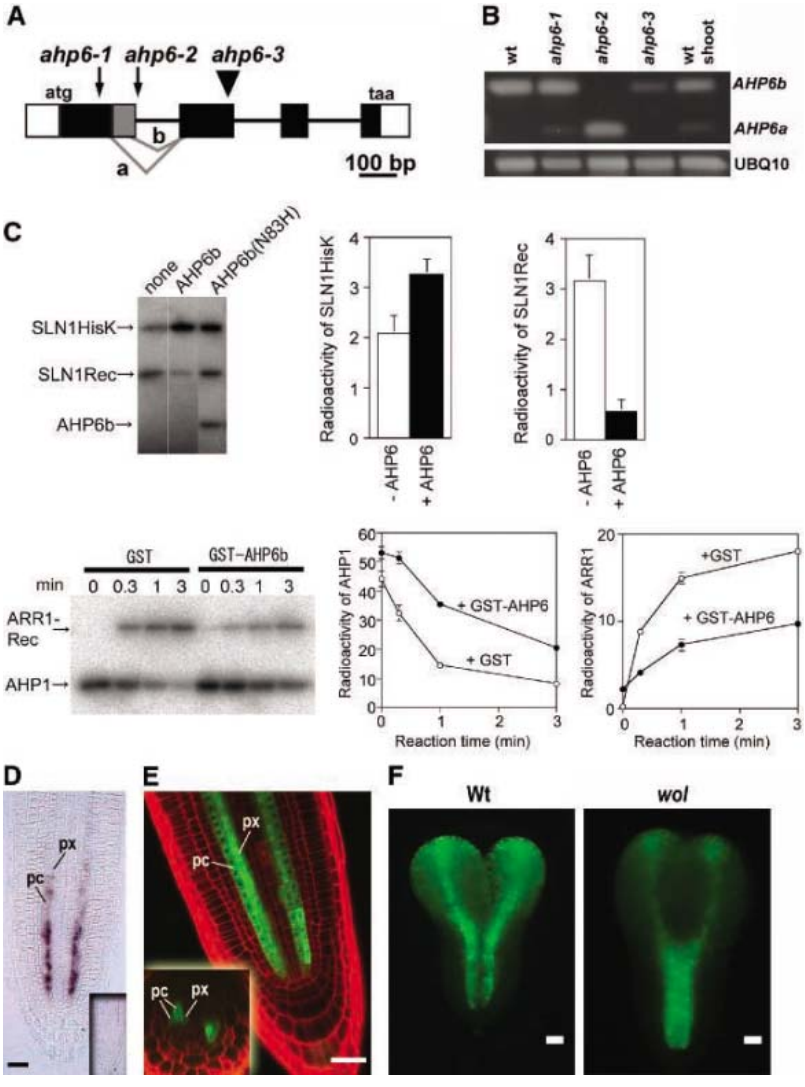

Fig. 3. Molecular characterization of the *AHP6* locus. (**A**) Structure of the *AHP6* gene. White boxes, untranslated regions; gray lines, the alternative splicing between *AHP6a* (a) and *AHP6b* (b) variants. Locations of the *ahp6* mutations are shown by arrows (single nucleotide polymorphisms) or arrowheads (T-DNA insertion, stock number SALK_058085). (**B**) Analysis of both *AHP6* transcripts by reverse transcription polymerase chain reaction (RT-PCR). *UBQ10* is an internal control. The smaller transcript only becomes apparent in wild-type and *ahp6-1* roots after a greater number of cycles (*12*). (**C**) AHP6 is a pseudo-HPt because of the lack of the conserved His. Upper panels demonstrate that AHP6 inhibits phosphorelay from the SLN1 histidine kinase domain (SLN1HisK) to the SLN1 receiver domain (SLN1Rec). Lower panels indicate that AHP6 inhibits phosphorelay from phosphorylated AHP1 to ARR1. Radioactivity is measured in relative units and each value was quantified from four independent reactions (standard deviation indicated). (**D** and **E**) *AHP6* is expressed in protoxylem and adjacent pericycle cells as shown by in situ hybridization and with the *AHP6prom::GFP* reporter construct. The sense *AHP6* probe did not reveal any signal (inset). px, protoxylem; pc, pericycle. (**F**) *AHP6prom::GFP* expression during embryogenesis in early torpedo stage of wild-type and *wol* embryos. Scale bars, 20 μm.

cytokinin, the loss-of-protoxylem phenotype was enhanced (figs. S2A and S4B), supporting the role of AHP6 as a negative regulator of cytokinin signaling and implicating additional unidentified factors.

cre1 ahk3 shows intermediate cytokinin responsiveness (*17*). Histological studies revealed that 91% of *cre1 ahk3* roots (n = 35; wild type 0%, n = 50) had one or more extra protoxylem files, even though the number of procambial cell files remained normal (Fig. 1B) (*cre1 ahk3*: 32.6 ± 2.0 cells, n = 17; wild-type: 31.8 ± 2.2 cells, n = 20; errors are SD). Similar phenotypes are observed in weak *CRE1prom::CKX2* lines (fig. S3B). To investigate whether the ectopic protoxylem files in these genotypes are due to an increase in the spatial domain of AHP6 action, we first studied the expression of *AHP6* in *cre1 ahk3*. Consistent with this, the *AHP6* expression domain is slightly broader than in wild-type roots, because it is typically found in two (as opposed to one) protoxylem cell files and in three (as opposed to two) adjacent pericycle cell files (88%; n = 17) (Fig. 4A). This expanded domain of *AHP6*

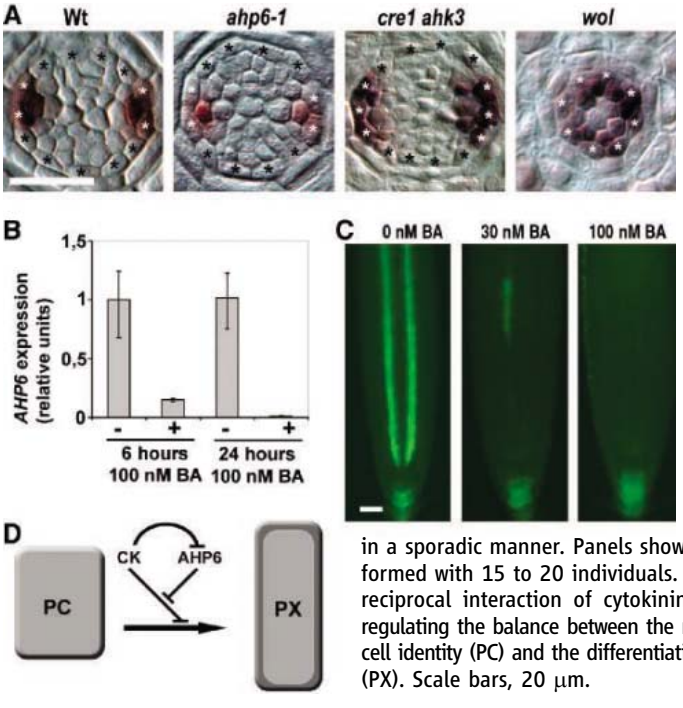

Fig. 4. Cytokinin negatively regulates AHP6 expression. (**A**) The expression domain of *AHP6* broadens in genetic backgrounds with decreased cytokinin signaling. White asterisks, pericycle cells expressing *AHP6*; black asterisks, other pericycle cells. (**B**) *AHP6* expression is down-regulated following cytokinin treatments as shown by real-time quantitative PCR. Error bars show means ± SD. (**C**) With intermediate cytokinin concentrations *AHP6* is expressed in a sporadic manner. Panels shown represent analyses performed with 15 to 20 individuals. (**D**) A model showing the reciprocal interaction of cytokinin signaling and AHP6 in regulating the balance between the maintenance of procambial cell identity (PC) and the differentiation of protoxylem elements (PX). Scale bars, 20 μm.

expression is responsible for the *cre1 ahk3* phenotype, because loss of AHP6 function in *ahp6-1 cre1 ahk3* was able to suppress the ectopic protoxylem (91%; $n = 45$) (Fig. 1B). In both *wol* and *cre1 ahk2 ahk3*, the *AHP6* expression pattern expands throughout the vascular bundle (Fig. 4A) (*12*). The expanded expression pattern in *wol* is already evident by the early torpedo stage of embryogenesis when it occupies one broad domain within the embryonic root as opposed to two narrow strands in wild-type (Fig. 3F and fig. S8C). This indicates that cytokinin signaling specifies the spatial domain of *AHP6* expression upstream of protoxylem differentiation, which occurs after embryogenesis. Next, we examined the effect of exogenous cytokinins on *AHP6* expression. We observed down-regulation of the *AHP6* transcript after a 6-hour treatment with cytokinins (Fig. 4B). Likewise, the level of fluorescence in the *AHP6prom::GFP* line was reduced by cytokinins, and the reduction occurred at lower levels of cytokinin in *ahp6-1* than in wild-type roots. (Fig. 4C and fig. S9). In the absence of applied cytokinin, the levels of *AHP6* transcript in *ahp6-1* were slightly lower than in the wild type (*12*).

We report a regulatory circuit between cytokinin signaling and its newly identified inhibitor, AHP6, which specifies the meristematic versus differentiated nature of procambial cell files (Fig. 4D). In this sense, our results are consistent with requirement of cytokinins for transdifferentiation of xylem observed in *Zinnia* mesophyll cell culture (*5*, *19*). AHP6 can be considered the founding member of a new "pseudo" subclass of HPt proteins within the wider group present in prokaryotes and eukaryotes.

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Materials and Methods
SOM Text
Figs. S1 to S9
References

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Fishing, Trophic Cascades, and the Process of Grazing on Coral Reefs

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Since the mass mortality of the urchin *Diadema antillarum* in 1983, parrotfishes have become the dominant grazer on Caribbean reefs. The grazing capacity of these fishes could be impaired if marine reserves achieve their long-term goal of restoring large consumers, several of which prey on parrotfishes. Here we compare the negative impacts of enhanced predation with the positive impacts of reduced fishing mortality on parrotfishes inside reserves. Because large-bodied parrotfishes escape the risk of predation from a large piscivore (the Nassau grouper), the predation effect reduced grazing by only 4 to 8%. This impact was overwhelmed by the increase in density of large parrotfishes, resulting in a net doubling of grazing. Increased grazing caused a fourfold reduction in the cover of macroalgae, which, because they are the principal competitors of corals, highlights the potential importance of reserves for coral reef resilience.

Caribbean reefs were acutely disturbed in 1983 when the herbivorous urchin *Diadema antillarum* experienced mass disease-induced mortality (*1*). In the absence of *Diadema*, parrotfishes (Scaridae) have become the dominant grazer on most Caribbean reefs (*2*). Grazing performs several critical functions in this ecosystem, including the conversion of primary production to fish-based trophic pathways (*3*), the provision of suitable settlement substrata for new corals (*4*), and the mediation of competition between corals and macroalgae (*5*). Parrotfishes are exploited in many parts of the region, and several studies have reported increases in their density when fishing intensity was reduced inside reserves (*6*, *7*). However, although reserves may benefit parrotfish populations in the short term, these impacts may be reversed on longer time scales. Most reserves aim to restore the biomass of large piscivores (*8*) such as the Nassau grouper (*Epinephelus striatus*), but this might eventually cause cascading top-down limitation on the biomass of their prey (*9*, *10*), which includes parrotfishes (*11*, *12*). Therefore, with the continued scarcity of *Diadema* (*13*), the realization of a successful reserve may impair levels of grazing and its associated ecosystem functions.

Few reserves are either large, old, or effective enough to have had a significant impact on large predators (*6*, *14*). An exception is the Exuma Cays Land and Sea Park (ECLSP), which lies near the center of the Bahamas archipelago. The ECLSP is large (456 km^2) and was established in 1959. A ban on fishing has been enforced there since 1986, and the current biomass of *E. striatus* is seven times greater in the ECLSP than that observed in three other regions of the archipelago (*15*). The ECLSP is, therefore, one of the few places in the Caribbean where the long-term impacts of reserves can be investigated (*16*). We sampled four island systems at hierarchical scales and contrasted the results in and around the reserve with those found at equivalent spatial scales in systems that lacked reserves. Specifically, fish communities of *Montastraea* reefs were sampled at scales of sites (hundreds of

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meters, n = 3 to 4), reefs (or reserve) (tens of kilometers, n = 3), and island systems (hundreds of kilometers, n = 4). The reserve is located between two nonreserve reefs, to the north and to the south of the reserve, in the Exuma Cays island system. To examine the influence of reserves on grazing, we created and tested a model of parrotfish grazing intensity that was sensitive to species, size, and life phase (*16*).

The overall biomass of all parrotfish predators within the reserve was approximately double that found in nonreserve areas within the same reef tract and was more than five times greater than that in other regions of the archipelago (Fig. 1). *E. striatus* accounted for 45% of this predator biomass, with the remainder being composed of other large groupers, including *Mycteroperca tigris* (27%) and a combination of Sphyraenidae, Muraenidae, and large Lutjanidae (28%).

At the scale of reefs within an island system (tens of kilometers), the community structure of parrotfishes showed significant variation only between the reserve and its immediate nonreserve reefs (analysis of similarities, R = 0.29, $P < 0.05$). Several parrotfish species exhibited significant differences in size across reserve boundaries (Fig. 2). Individuals of the smaller bodied scarid species, whose maximum length rarely exceeds 23 cm (*Scarus iserti* and *Sparisoma aurofrenatum*), were smaller inside the reserve (Fig. 2), but their densities were indistinguishable from those elsewhere [analysis of variance (ANOVA), $P > 0.05$]. In contrast, scarids that reached consistently large adult sizes, such as the terminal-phase (TP) males of *Sc. vetula* and *Sp. viride*, exhibited no difference in their size across the reserve boundary (Fig. 2), but their mean density was nearly doubled inside the reserve. Parrotfishes that occupied a wide range of size categories (6 to 32 cm) were either larger in the reserve [*Sp. viride* intermediate phase (IP)] or larger outside the reserve (*Sc. vetula* IP). Mean parrotfish sizes outside the reserve did not differ from those found elsewhere in the archipelago ($P > 0.05$).

Large-bodied parrotfishes appear to escape predation by the dominant piscivore, *E. striatus* (Fig. 3). The distribution of mouth sizes in the grouper population is such that few groupers (typically <0.5 individuals per 1000 m^2) are large enough to swallow TP parrotfish of the larger bodied species *Sc. vetula* and *Sp. viride* (Fig. 3), and such large groupers were observed only in the reserve. In contrast, between 60 and 90% of the *E. striatus* in the reserve are able to consume adults of the smallest bodied parrotfish, *Sc. iserti*, and 30 to 60% of groupers are able to swallow the medium-sized scarid, *Sp. aurofrenatum*. Adults of both parrotfish species were significantly smaller inside the reserve (Fig. 2). An increase in natural predator-caused mortality within the reserve would be expected to reduce their average longevity and therefore length (*17*) and grazing capacity (*18*).

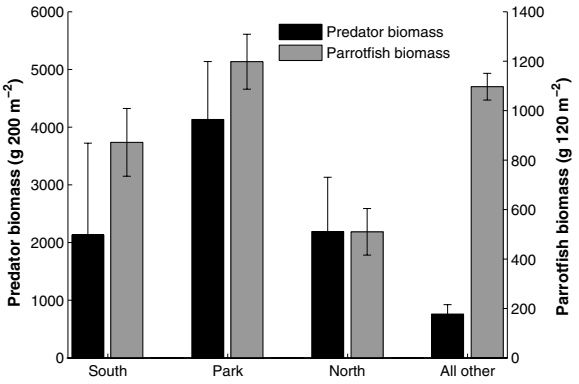

Fig. 1. Patterns of parrotfish biomass and their predators (±SE) within the Exuma Cays and for all other surveyed areas combined. "Park" denotes the ECLSP.

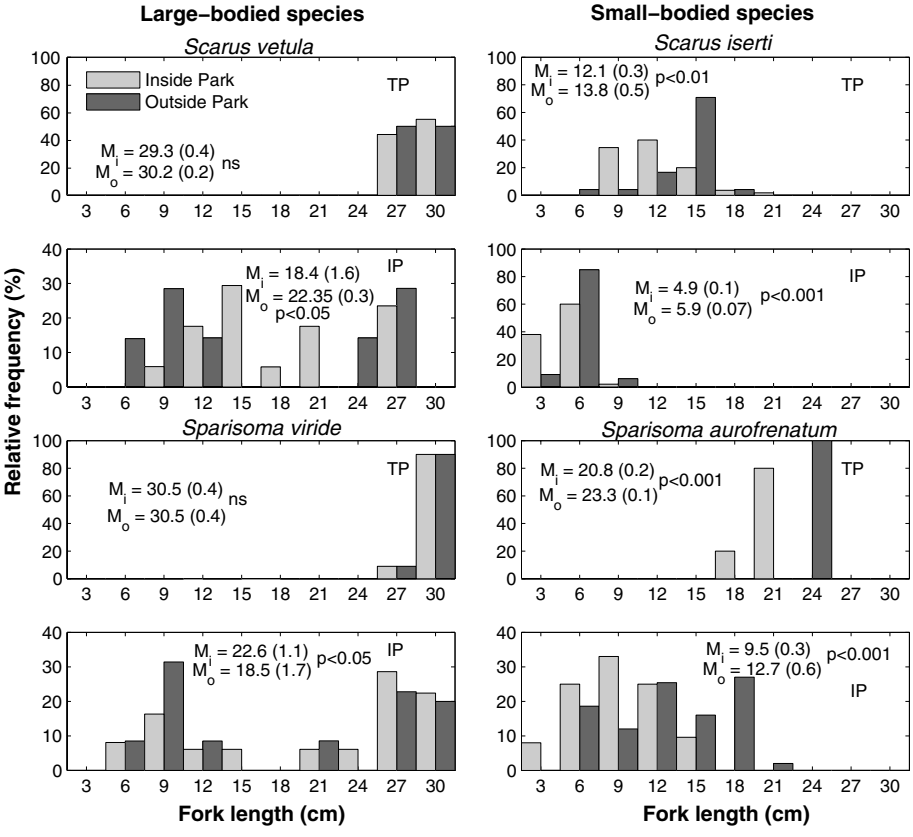

Fig. 2. Relative size frequency distributions of four parrotfish species in two life phases (TP and IP). Data were pooled for the *Montastraea* reef habitat inside and outside the ECLSP. Also shown are the mean (±SE) length of species inside (M_i) and outside (M_o) the reserve and the probability of a t test finding no significant difference between sites. "Fork length" is measured from the snout to the fork of the tail.

The optimal size of prey for many piscivorous fishes is 0.6 times that of the predator's jaw width (*19*); chasing larger prey may be uneconomic because of the greater evasive potential of larger individuals (*20*). Therefore, predator capacity was also plotted for the assumption that prey choice was restricted to the most preferred individuals [those with body height not exceeding 60% of grouper jaw width (Fig. 3)]. Under this scenario, a grouper's capacity to consume the smaller bodied species remains greater in the reserve, whereas the likelihood of consuming TP *Sc. vetula* or *Sp. viride* is even less, emphasizing the potential for a size escape from predation. However, foraging by *E. striatus* is primarily nocturnal and crepuscular (*12*, *21*) and is therefore coincident with the nocturnal resting of parrotfishes (*22*), often in vulnerable locations on the reef. Prey may be much less likely to escape under these circumstances, thereby increasing the probability that groupers will prey on scarids with dimensions approaching the upper limits of mouth size (though it appears that *Sc. vetula* and *Sp. viride* are able to avoid this increased vulnerability).

Our data suggest that the fishing mortality of large-bodied parrotfish is considerable in

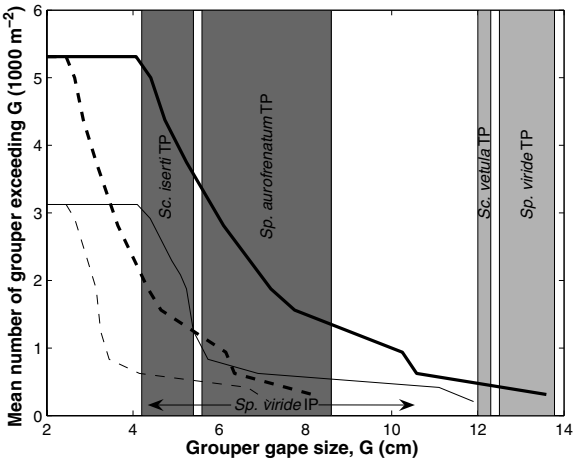

Fig. 3. Consumptive capacity of Nassau grouper populations inside (bold lines) and outside (light lines) the ECLSP. Solid lines assume that prey consumption is constrained by the full width of grouper mouthparts, whereas dotted lines represent an optimal prey size equivalent to 60% of the full gape. Dorsoventral heights of parrotfish (prey) species were plotted for the observed range of scarid size in the Exuma Cays. Dark and light shading denote the size ranges of small- and large-bodied parrotfishes, respectively.

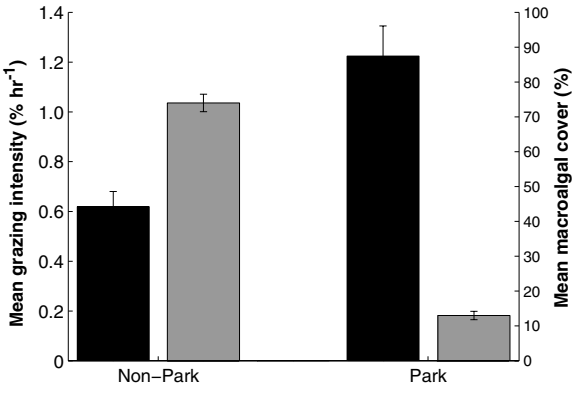

Fig. 4. Mean grazing intensity of parrotfishes (black bars) and macroalgal cover (gray bars) (±SE) inside and outside the ECLSP. Reserve impacts are significant ($P < 0.01$) for each variable.

fished areas of the Exuma Cays. Of the large commercial fishing vessels registered as using fish traps in the Bahamas, 40% (*14*) have sufficient size (>10 m) and proximity (Nassau to Exuma Cays) to fish around the reserve (*23*). An additional 30 traps are deployed locally to the south of the reserve. Large-bodied parrotfish are highly susceptible to fish traps (*6*), which may be left unattended during periods of high winds and cause considerable, though not quantified, mortality of parrotfishes. Studies in Barbados found traps to be disproportionately selective for *Scarus vetula* (*6*), and the biomass of this species was almost seven times greater inside the reserve. Overall, the total biomass of parrotfishes was significantly greater inside the reserve (Fig. 1, $P < 0.001$). We conclude, therefore, that larger parrotfishes have benefited numerically from a reduction in fishing pressure within the ECLSP.

The results of nested analyses allow us to infer that the reserve has significant effects on predator biomass and on the community structure, size distribution, and grazing intensity of parrotfishes. Even if we assume that only 2 of the 12 inter-reef comparisons exhibit significant differences, the probability that both involve the reserve is ~1%. Fully functioning marine reserves in the Caribbean appear to have a negative impact on the size distribution of smaller bodied parrotfish through increased predation, but a positive impact on larger bodied species because of the release from fishing pressure. With the continued paucity of *Diadema* (*13*) and the nonlinear positive relationship between fish length and grazing intensity (*18*), any impact on larger bodied fishes will have a disproportionately large impact on grazing. In this system, the net impact of reserve implementation was a doubling of total scarid grazing (Fig. 4), and this reef-level effect was observed only across reserve boundaries (nested generalized linear model ANOVA, $P < 0.05$).

The cover of living coral on Bahamian reefs was severely reduced by bleaching during the exceptionally high sea temperatures of the 1998 El Niño–Southern Oscillation event (*13*). Given projected climate change, the resilience, or ability of reefs to recover from such disturbances, is a key societal concern (*24*). Recovery requires the successful recruitment and survival of new corals, but both processes are inhibited by macroalgae (*5*, *25*). Our data reveal a strong negative relation between fish grazing intensity and macroalgal cover in the Exuma Cays; the cover of macroalgae was reduced fourfold inside the reserve (Fig. 4), whereas there were no reef-scale fluctuations in cover in systems with no reserve ($P > 0.40$). Although the biomass of herbivorous fishes has been negatively correlated with macroalgal cover on a Caribbean-wide scale (*26*), the direct small-scale impacts of a reserve were previously undocumented. Although reductions in macroalgal cover inside reserves may enhance the recruitment and survival of corals, elevated parrotfish grazing may have complex impacts on reefs. Scarid grazing is an important source of bioerosion, and although only 4% of their bites are taken from adult corals (*18*), the role of parrotfishes as predators of juvenile corals is yet to be evaluated.

The "benefits" accrued from a reserve will largely depend on the intensity of fishing outside its boundaries. If Caribbean parrotfishes were not affected by exploitation at all, then a reserve would cause only negative impacts on parrotfishes because of enhanced predation. Rescaling the size of each parrotfish using the mean size discrepancies reported in Fig. 2, we calculate that the total grazing intensity would drop by 4 to 8% of its current value in several island systems (San Salvador, the Turks and Caicos Islands, and Andros) where parrotfish exploitation is relatively light (fish traps are used on <1% of fishing trips). A predation-based reduction in grazing of 4 to 8% would be fully compensated for if the reserve enabled parrotfish densities to increase by a mean level of 9% (approximately one individual of each life phase of each species in 1200 m^2). To place this reserve impact in perspective, it represents just one-sixth that observed in the Exuma Cays, which by Caribbean standards is a relatively lightly fished system. For example, scarid grazing intensity in fished regions of the Exuma Cays was at least five times greater than in exploited areas of Jamaica (*16*). Because parrotfish form bycatch in fisheries and are easily targeted by commercial and recreational spear fishermen, reserves will almost always increase the level of fish grazing within their boundaries.

Many fisheries management agencies are adopting the principle of ecosystem-based management (EBM), in which the wider functioning and requirements of whole ecosystems are considered (*27*). Despite the appealing premise of EBM, its implementation is generally constrained by a lack of data or appropriate analyses. How do EBM tools, such as marine reserves, influence the key processes that drive an ecosystem? This question is particularly important when considering disturbed systems, because returning one process to its "natural" level may have unexpected and even deleterious consequences for the ecosystem overall. Our results indicate that the long-term impact of Caribbean no-take marine reserves is enhanced grazing, a process that is key to the ecosystem functioning of coral reefs.

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Acknowledgments, including complete funding information, should be gathered into a brief statement at the end of the references and notes.

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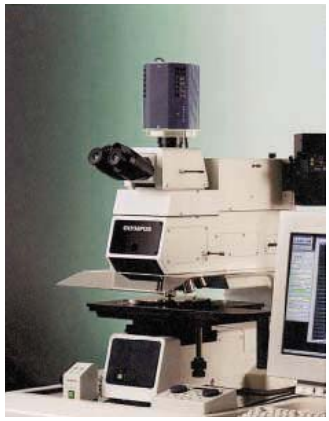

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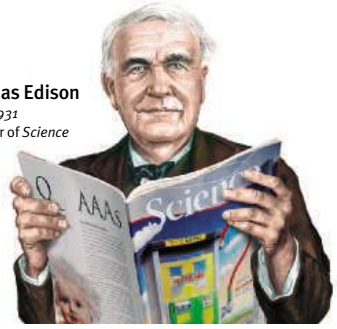

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POSITIONS OPEN

Drexel UNIVERSITY

The Department of Bioscience and Biotechnology at Drexel University invites applicants for a **TENURE-TRACK POSITION** in the Division of Nutrition and Food Science. The successful candidate must have a Ph.D. in nutrition or a related field and will take a leading role in the division, which is doing dynamic research in basic and clinical nutrition sciences. The candidate must have a strong research program, peer-reviewed publications, and a track record of extramural funding. The candidate will teach at both the graduate and undergraduate levels. Drexel University is located in the heart of Philadelphia, close to other major universities, and has a diverse array of cultural activities. Please send curriculum vitae and a statement of research and teaching interests to: **Dr. Cecilie Goodrich, Chair, Search Committee for Division of Nutrition and Food Science Candidate, Department of Bioscience and Biotechnology, Drexel University, 3141 Chestnut Street, Philadelphia, PA 19104.**

ENVIRONMENTAL CHEMIST

The Skidaway Institute of Oceanography invites applications for a faculty position at the Assistant Professor level in environmental chemistry or geochemistry, with interests in contaminant chemistry and coastal environments. The successful candidate must have a Ph.D. and is expected to develop a vibrant, individual, collaborative, and societally relevant research program. Pertinent areas of research include, but are not limited to: aquatic toxicology, chemical mechanisms of environmental exposure, fate, reactivity, transport and impact of metals or organic compounds in coastal systems; mechanisms of toxicant-macromolecule interactions. We seek faculty whose interests complement existing strengths in marine chemistry and geochemistry, microbial ecology, coastal geology and physics, and who are interested in developing research programs that exploit the unique physical setting of the Institute. The Skidaway Institute of Oceanography is strategically located near Savannah, Georgia, providing direct access to and infrastructure for research in extensive salt marsh, estuarine, and continental shelf environments. The candidate should be willing to participate in academic and nontraditional education and training programs. Additional information about the Institute and its programs is available at **website: http://www.skio.peachnet.edu.** Applications from more senior candidates may be considered in exceptional circumstances. Send curriculum vitae, statement of research and teaching experience and interests, and contact information for at least three references to: **Environmental Chemist Search, Skidaway Institute of Oceanography, 10 Ocean Science Circle, Savannah, GA, 31411.** Review of applications will begin on February 1, 2006, and will continue until the position is filled. *Equal Opportunity/Affirmative Action Employer.*

RESEARCH ASSOCIATE. Two NIH-funded postdoctoral positions in the Department of Physiology at the University of Texas Health Science Center at San Antonio (UTHSCSA) are immediately available. Research will focus on structure-function relations and regulation of the epithelial Na channel (ENaC). The Department of Physiology is a strong research community with many opportunities for collaboration and development of laboratory skills. San Antonio is an attractive, historic city that is affordable and has a multicultural heritage. Applicants should hold a Ph.D. or equivalent with strong electrophysiology background. Please send curriculum vitae and names and addresses of three references to: **Dr. James Stockand, Department of Physiology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900. E-mail: stockand@uthscsa.edu.**

All postdoctoral appointments are designated as security sensitive positions. The UTHSCSA is an Equal Employment Opportunity/Affirmative Action Employer.

POSITIONS OPEN

THE CHINESE UNIVERSITY OF HONG KONG

The Department of Physiology invites applications for the post of **ASSISTANT PROFESSOR,** Post One (Ref. 05/204(665)/2) (closing date: 27 January 2006). Applicants should have (1) a relevant Ph.D. degree; (2) three to four years of postdoctoral experience; and (3) a strong research record in one of the following areas: neurosciences and brain research; cardiovascular biology and medicine; or stem cell biology and molecular endocrinology. Applicants with strong molecular background and/or experience with systems-level function, stem cell biology, and electrophysiological techniques are particularly welcome. The appointee will (1) teach undergraduate and postgraduate courses; and (2) apply his/her expertise in one of the aforementioned areas so as to complement and strengthen the Department's existing research and teaching activities. Appointment will initially be made on a fixed-term contract basis for up to two years from June 2006 or as soon as possible thereafter, renewable subject to mutual agreement.

The Department of Surgery invites applications for the post of **POSTDOCTORAL FELLOW / RESEARCH ASSOCIATE,** Post Two (Ref. 05/203(665)/3) (closing date: 31 January 2006). The Department is well equipped with cell and tissue cultures, genetic and molecular research equipment and facilities for animal experiments. Applicants should have a Ph.D. degree with a background in biomedical research (for Postdoctoral Fellow) or a Master's degree with four years of postqualification working experience in a related field (for Research Associate). The appointee will assist in research projects on surgical problems, including the field of cancer research using cellular and molecular approaches, and will work at the Prince of Wales Hospital, the teaching hospital of the University. Appointment will initially be made on a fixed-term contract basis for one to two years, renewable subject to mutual agreement. Salary will be highly competitive, commensurate with qualifications and experience.

The University offers a comprehensive fringe benefit package, including medical care, plus for Post One: a contract-end gratuity for an appointment of two years and housing benefits for eligible appointees. Further information about the University and the general terms of service for appointments is available at **website: http://www.cuhk.edu.hk/personnel.** The terms mentioned herein are for reference only and are subject to revision by the University. Please send full resume, copies of academic credentials, a publication list and/or abstracts of selected published papers (for Post One only), together with names, addresses, and fax numbers/e-mail addresses of three references to whom applicants' consent has been given for their providing references (unless otherwise specified), to: **Personnel Office, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong (fax: 852-2603-6852)** by the respective closing dates. The Personal Information Collection Statement will be provided upon request. Please quote the reference number and mark Application - Confidential on cover.

POSTDOCTORAL POSITION

A Postdoctoral Position is available immediately in the laboratory of **Maurizio Bocchetta** at the Loyola University Chicago Medical Center, Illinois. The successful candidate will study the role of Notch signaling in the pathogenesis of malignant mesothelioma and lung cancer. Candidates must have a background in molecular and cellular biology. Salary dependent upon experience. The Medical Center is 10 minutes from Oak Park, a beautiful small town internationally famous for its architecture, and 20 minutes from downtown Chicago. Send or fax curriculum vitae and names of three references (at least one United States reference) to: **Maurizio Bocchetta, Ph.D., Cardinal Bernardin Cancer Center, Room 204, 2160 South First Avenue, Maywood, IL 60153 U.S.A. Fax: 708-327-3238. E-mail: mbocche@lumc.edu.**

Tenure/Tenure Track Position
National Institute of Allergy and Infectious Diseases (NIAID)
Department of Health and Human Services
National Institutes of Health

The Laboratory of Intracellular Parasites (LICP), National Institutes of Allergy and Infectious Disease (NIAID), National Institutes of Health (NIH), Rocky Mountain Laboratories (RML), Hamilton, Montana, has a tenure-track position available to pursue independent studies on the immunology of biodefense (BD) bacterial pathogens. This initiative will expand upon existing host-pathogen interactions research programs in LICP studying *Coxiella, Francisella, Brucella, Rickettsia, and Salmonella*. Preference will be given to those candidates with an interest in *Rickettsia*, and/or experience in animal models of infection and immunity. The overall goals of the program will be to investigate immunity in pre-clinical models of infection and disease, define protective immune mechanism(s) and antigens, and apply this information towards immune intervention strategies. The candidate will be expected to incorporate modern molecular, biochemical, and genetic technologies in immunology, animal modeling, and vaccine development to accomplish these goals.

The Rocky Mountain Laboratories offers state-of-the-art core facilities for genomics, proteomics, DNA microarray, and biological imaging in a recently renovated modern laboratory setting. A new BL3 containment building with animal capacity is available. Candidates must hold a Ph.D, D.V.M, or M.D. degree and have a minimum of 2 years post-doctoral experience in relevant areas of investigation. Resources and appointment mechanism will be commensurate with experience.

The NIH Rocky Mountain Laboratories supports research on a number of significant bacterial and viral human pathogens including *Borrelia, Brucella, Burkholderia, Chlamydia, Coxiella, Francisella, Salmonella, Staphylococcus, Streptococcus, Yersinia*, retroviruses, HIV, and transmissible spongiform encephalopathies (TSE). The laboratory is located in the scenic Bitterroot Valley of western Montana with easy access to some of the finest outdoor recreational opportunities in North America.

Application Process: Applicants must be U.S. citizens, resident aliens, or nonresident aliens with or eligible to obtain a valid employment authorized visa. Salary depends on degree and qualifications. Other incentives may be available. Applicants must send curriculum vitae, bibliography and a detailed statement of research interests (1-2 pages). In addition, three letters of recommendation must be sent directly from the referees. Please note search #001 when sending materials. All materials may be sent via email to **Felicia Braunstein at braunsteinf@niaid.nih.gov** or by US Mail to**: Frank Gherardini, Ph.D., Chairperson, NIAID Search Committee, c/o Ms. Felicia Braunstein, DIR Committee Manager, 10 Center Drive MSC 1349, Building 10, Rm. 4A-30, Bethesda, Maryland 20892-1349**. Completed applications **MUST** be received by **February 1, 2006**. For additional information on this position, and for instructions on submitting your application, please see our website at: **http://healthresearch.niaid.nih.gov**. All information provided by applicants will remain confidential and will only be viewed by authorized officials of the NIAID.

WWW.NIH.GOV

Tenured/Tenure-Track/Senior Scientist Positions

The National Eye Institute (NEI) at the National Institutes of Health is seeking outstanding and creative scientists for several Tenured, Tenure-Track and Senior Scientist positions as part of a new multidisciplinary initiative for therapy of retinal genetic neurodegenerations. The program will be located within the Institute's Division of Intramural Research NEI, National Institutes of Health (NIH), Department of Health and Human Services (DHHS). These positions offer an opportunity to participate in an organization dedicated to uncovering new scientific knowledge, both basic and clinical, and ensuring the translation of that knowledge to the treatment of ocular diseases.

Investigators chosen for this Program will have access to clinical resources and research programs of the NEI as well as the intellectual and technical resources of the entire NIH. Investigators are expected to provide scientific leadership and expertise in one or more disciplines that include genetics, gene therapy, molecular biology, cellular biology, physiology, developmental neurobiology, or animal studies as they relate to the design and conduct of pre-clinical and clinical therapeutic retinal genetic disease research. The basic science components will interface with the existing clinical expertise within NEI on ophthalmic genetic diseases.

This will be a comprehensive program to move into human therapy. The following approaches are pertinent to this effort: molecular genetic analysis of fundamental questions in retinal disease; biochemistry of transcriptional regulation; genetic basis of cellular differentiation and pattern formation in a multicellular tissue; molecular and cellular mechanisms of retinal development and their role in the progression and treatment of retinal degenerative diseases; molecular basis of cell-cell interactions that regulate retinal neurogenesis and neuronal specificity during development and regeneration; pre-clinical animal models for retinal degenerative diseases; pharmacogenetics; cell-based therapies; molecular control of stem cell neurobiology and self-renewal; neural remodeling in retinal degenerative diseases.

Salary is commensurate with research experience and accomplishments. A full Federal package of benefits is available (including retirement, health, life and long term care insurance, Thrift Savings Plan etc). Applicants should submit curriculum vitae, bibliography, copies of three major publications, a summary of research accomplishments, a brief statement of future research goals, and three reference letters to:

Sheila Ayala, Intramural Administrative Specialist, Office of the Scientific Director, National Eye Institute, 31 Center Drive, Building 31, Room 6A22, Bethesda, MD 20892, Tel: 301-451-6763, Email: sayala@nei.nih.gov.

This position will be open until filled.

Health Research in a Changing World

Fighting Diseases and Improving Lives

Tenure Track Position in Bacterial Pathogenesis
Laboratory of Clinical Infectious Diseases
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health & Human Services

The National Institute of Allergy & Infectious Diseases (NIAID), Division of Intramural Research (DIR), Laboratory of Clinical Infectious Diseases (LCID) is seeking an outstanding investigator to develop a clinical and basic program in bacterial pathogenesis.

The LCID studies the pathogenesis, pathophysiology, treatment and prevention of infectious diseases, including emerging infections and pathogens that are of concern in biodefense, as well as microorganisms that cause persistent, recurrent, or fatal disease. Current areas of clinical and basic expertise in the LCID include viral, fungal, and mycobacterial pathogenesis and pathophysiology and the pathophysiology of defects in cellular apoptosis.

The successful candidate will establish an independent research program in bacterial pathogenesis with both laboratory and clinical components. The incumbent will develop clinical protocols, which may include natural history, pathophysiology, mechanism of action, treatment, or all of the above. Board eligibility/board certification or the equivalent in Internal Medicine or Pediatrics and Infectious Diseases or Allergy and Immunology are desirable, but Ph.D.'s with active clinical programs are also encouraged to apply. Sufficient independent resources including space, support personnel and an annual budget for services, supplies and salaries have been committed to the position to ensure success.

The appointment is a Tenure Track appointment and will be at the appropriate level under Title 42, which is equivalent to a University Assistant Professor rank. Salary is dependent on experience and qualifications.

Interested candidates may contact Dr. Steven Holland, Chief, LCID, DIR, and NIAID at 301/402-7684 or email (smh@nih.gov) for additional information about the position.

To apply for the position, candidates must submit a curriculum vitae, bibliography, three letters of reference, a detailed statement of research interests, and reprints of up to three selected publications by January 31, 2006 to Patrick Murray, Ph.D., Chair, NIAID Search Committee, c/o Mrs. Lynn Novelli, Committee Manager, 10 Center Drive, MSC 1356, Building 10, Room 4A26, Bethesda, Maryland 20892-1356. Further information on this position and guidance on submitting your application is available on our website at: http://healthresearch.niaid.nih.gov/science

Please reference "Science" on your resume.

Positions @ NIH
THE NATIONAL INSTITUTES OF HEALTH

Chief, Laboratory of Pathology

The Center for Cancer Research (CCR), National Cancer Institute (NCI), National Institutes of Health (NIH), Department of Health and Human Services (DHHS), is seeking an outstanding physician-scientist to serve as Chief of the Laboratory of Pathology (LP) located on the campus of the NIH in Bethesda, Maryland. The successful candidate will oversee:

- the pathology clinical operations at the Clinical Research Center which serves the entire NIH patient community
- a clinical research program that applies advanced technology to biospecimen research
- an ACGME-accredited 4-year program in anatomic pathology.

This position provides a qualified candidate the opportunity to craft a world-class pathology program in a multidisciplinary translational research environment located in the new NIH Clinical Research Center, the largest clinical research center in the world. Resources available are substantial and include over one hundred staff positions across a full range of clinical research operations including, staff clinicians, principal investigators, staff scientists, medical technologists, technicians, clerical and administrative support, as well as fellowship trainees. These positions are fully funded including salary, awards, and a generous federal government benefits package.

The CCR is the largest component of the intramural biomedical research enterprise at NIH. Areas of emphasis within the CCR that interface seamlessly with the Laboratory of Pathology include molecular targets and oncology, immunology and immunotherapy, advanced imaging and biomarkers, HIV/AIDS, systems biology, genetics and genomics. The clinical pathology program and other CCR areas of focus are supported by a strong foundation in advanced biomedical technologies, enhanced opportunities for collaborations within and between interdisciplinary and multidisciplinary research teams, and an agile infrastructure that promotes a dynamic translational research process.

The Chief of the Laboratory of Pathology will oversee diagnostic anatomic pathology for patients undergoing clinical trials in the NIH Clinical Research Center, for all patients being considered for entry into clinical trials, and for epidemiologic and case studies of disease pathophysiology. Clinical diagnostic services include surgical pathology, cytogenetics, cytopathology, postmortem, hematopathology, pediatric pathology, electron microscopy, flow cytometry, and specialized histology. The Chief will oversee expert consultation in the fields of hematopathology, OB/GYN pathology, cytopathology, and pediatric pathology to the extramural medical community.

The Pathology Chief will guide the establishment of a research program and develop science-based evidence for best practices in procurement and process clinical research specimens in collaboration with the major clinical services and the newly formed Clinical Molecular Targets Core and Biospecimen Procurement and Processing Facility. In addition, CCR will support the successful candidate in the conduct of research in his/her area of interest.

Position Requirements:

Candidates must have an M.D. degree, be board-certified in pathology, have managerial experience overseeing pathology service delivery, have demonstrated an ability to work collaboratively, and have an in-depth knowledge of--and interest in--biospecimen research as it applies to the development of science-based rationale for procurement and processing. Salary is commensurate with experience. All applicants should submit a letter indicating interest in the position, a statement of research interests, a career synopsis and brief bibliography, current curriculum vitae and complete bibliography, and the names and addresses of five references.

Applications should be sent to: Richard Alexander, M.D., c/o Randy Redmond, National Cancer Institute, 31 Center Drive, Suite 3A19, Bethesda, Maryland 20892

Branch Chief Positions

National Human Genome Research Institute

The National Human Genome Research Institute (NHGRI) of the National Institutes of Health (NIH) is seeking one or two dynamic and experienced senior investigators to serve as Branch Chiefs in its Intramural Program. The Division of Intramural Research at NHGRI is a world-class, highly collegial research environment, where basic and clinical research is performed in a highly integrative fashion in the broad areas of genetics, genomics, diagnostics, and therapeutics.

The successful candidate(s) will have significant leadership responsibilities, involving the oversight of an existing cadre of investigators with research programs in human genetics, developmental genetics, chromosome biology, gene therapy, immunology, neuroscience, and stem cell biology as well as leading future recruitment efforts. A vision for crafting cutting-edge research programs that advance the frontiers of genetics and genomics will be key. In addition to superlative scholarship, the successful candidates must have well-honed administrative skills to lead a large and diverse research program.

These fully funded, tenured positions will include appropriate start-up allowances, an ongoing commitment of clinical and laboratory resources, and positions for support staff and trainees. In addition to the resources of the NIH Clinical Research Center, there will be full access to NHGRI core facilities. Candidates must have an M.D., Ph.D., or equivalent degree, as well as advanced training and demonstrated accomplishment in genetic and/or genomic research.

Interested applicants should submit their curriculum vitae, a three-page description of their research program, and three letters of recommendation through our online application system, at http://research.nhgri.nih.gov/apply.

The closing date for these positions is March 1, 2006.

For more information about the NHGRI Intramural Program, please see http://www.genome.gov/DIR
Specific questions regarding these positions may be directed to Dr. Andy Baxevanis (Search Chair) at andy@nhgri.nih.gov or by fax (301-480-2634).

WWW.NIH.GOV

Division of Cancer Biology
Cancer Etiology Branch
Chemist/Microbiologist/Biologist

With nation-wide responsibility for improving the health and well being of all Americans, the Department of Health and Human Services (DHHS) oversees the biomedical research programs of the National Institutes of Health and those of NIH's research Institutes.

The National Cancer Institute (NCI) at the NIH is seeking a Chemist, Microbiologist, or Biologist to fill the position of Chief in the Cancer Etiology Branch (CEB). This branch administers a large portfolio of research grants covering a broad spectrum of topics directed at understanding the biological basis of cancer, emphasizing cancer etiology, biological and chemical carcinogenesis. The Branch Chief uses expert knowledge of the research field and administrative experience to provide the Branch with leadership, direction, coordination and perspective as well as to respond to NCI leadership. The Chief develops initiatives in the area of scientific responsibility, establishes program priorities, evaluates program effectiveness, provides information, advice and consultation to individual scientists and institutional management officials relative to NIH and NCI funding, provides NCI leadership with recommendations concerning funding needs, priorities and strategies, and organizes meetings and workshops to further program objectives.

A full Civil Service package of benefits (including health and life insurance options, retirement, paid holidays, vacation and sick leave) is available.

The NCI vacancy announcement for this position contains complete application procedures and lists all mandatory information, which you must submit with your application. To obtain the vacancy announcement for this position which will be available on **01/06/2006** and posted under announcement #**NCI-05-104816**, you may visit the website **https://www.usajobs.opm.gov**. Questions can be directed to **Eugene McDougal on (301) 435-5722**. Please see vacancy announcement for application submission requirements.

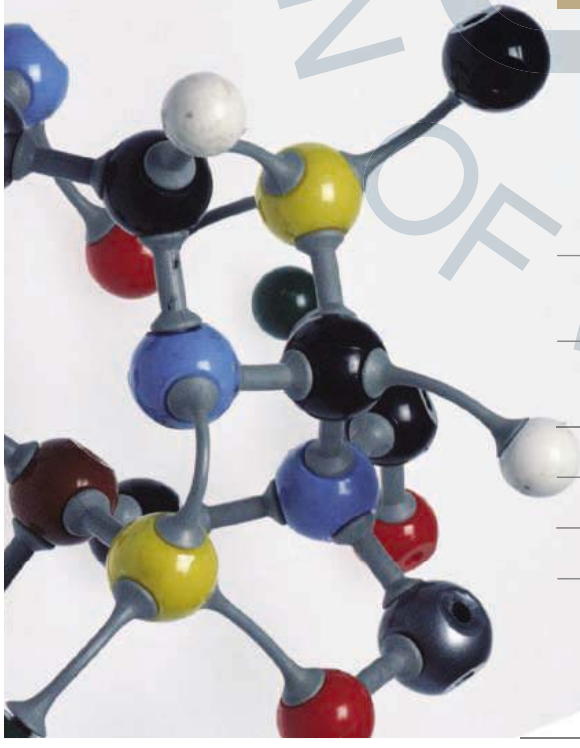
Branch Chief/Veterinary Medical Officer/
Animal Program Director

National Institute of Child Health and Human Development

Duties include: Direction of NICHD animal disease control programs, management of government staff and lab animal care contracts, responsibility for the animal program budget, serving on the ACUC, and assuring compliance with regulations and guidelines relevant to lab animal use and continued AAALAC accreditation

Qualifications: Doctor of Veterinary Medicine or equivalent degree at a school approved or accredited by the Veterinary Medical Association (AVMA), a State Department of Education, or a State Board of Veterinary Medical Examiners.

Applications must be received by **1/27/06**. Please send a letter describing your background and interests, and a curriculum vitae, and arrange for three letters of reference to be sent to: **Karl Pfeifer, Ph.D., Head, SGI/NICHD (kp74m@nih.gov)6 Center Drive, Bldg 6B, Rm 2B206, Bethesda, MD 20892**



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Office of Intramural Training and Education

University of Washington
College of Forest Resources

Faculty positions in:

- Environmental/Natural Resource Economics
- Quantitative Landscape Science
- Natural Resource Restoration and Management
- Bioresource Science

Surrounded by the beauty of the Pacific Northwest, the University of Washington has a 144-year tradition of academic excellence, scientific innovation, work/life balance, and a thriving arts and athletic community. The College of Forest Resources is undergoing an exciting transformation that focuses on the stewardship of natural and managed environments and the sustainable use of products and services. The unifying theme of sustainability means our interdisciplinary faculty integrate social/cultural, ecological, and economic measures in order to better lead, research, and educate the next generation of scientists, professionals, and leaders.

We are recruiting four tenure-track faculty at the assistant professor level (100% FTE, nine month appointment). These new faculty are expected to work in an interdisciplinary environment and to nurture and strengthen collaborations with other colleges and schools. Examples include our urban ecology, restoration network, stand management, and quantitative science programs. We invite broadly trained applicants with demonstrated research interests in environmental and natural resource sciences.

Applicants should have a demonstrated interest and ability to work in an interdisciplinary, collaborative applied setting. All positions involve teaching, research, and service responsibilities and successful candidates are expected to develop strong research programs in their disciplinary areas of expertise.

All positions require that candidates complete their Ph.D. by autumn 2006 when the positions commence. A letter of interest (including a statement of teaching experience and research interests), curriculum vitae, three letters of reference, and a writing sample or representative publication should be sent to: **cfrsrch@u.washington.edu**.

Environmental/Natural Resource Economics

We encourage applications of those interested in the economics of land use patterns and land cover changes; externalities or non-market valuation of environmental services; water conservation; or environmental regulation. Questions should be directed to **Professor Ivan Eastin, Chair, Environmental/ Natural Resource Economics Faculty Search Committee: (206) 543-1918** or **eastin@u.washington.edu**. Review of applications will begin **January 31, 200**6 and continue until the position is filled.

Natural Resource Restoration and Management

We seek a broadly trained scientist with a Ph.D. in plant or animal ecology, silviculture, horticulture, or a related area. Individuals with research interests and expertise in the management and restoration of ecological systems found from urban to wildland settings are sought. The successful candidate must have an emerging research and publication record plus demonstrated interests in program development, collaborative research, teaching, and outreach. Questions should be directed to: **Professor Thomas Hinckley, Chair, Natural Resource Restoration and Management Faculty Search Committee: (206) 543-1588** or **hinckley@u.washington.edu**. Review of applications will begin **February 16, 2006** and continue until the position is filled.

Quantitative Landscape Science

We encourage applications of those interested in the methods of quantitative analysis of landscapes and their application to problems of social and natural aspects of landscape change in ecosystems undergoing development and urbanization. The appointee will have many opportunities to collaborate across departmental and disciplinary programs to build a quantitative landscape program within their specialty at the University of Washington. The University is located in an area of rapid landscape change along an extensive urban-wildland interface and several interdisciplinary programs are currently engaged in teaching and research on this subject. Applicants with research interests and expertise in the application of current technologies and statistical approaches to the study of forest resources, ecology, biometrics, statistics, conservation biology, or geography (e.g., remote sensing, GIS, spatial/multivariate statistics, computational approaches to spatial problems) will be given the strongest consideration. Questions should be directed to: **Professor E. David Ford, Chair, Quantitative Landscape Science Faculty Search Committee: (206) 685-9995** or **edford@u.washington.edu**. Review of applications will begin **February 28, 2006** and continue until the position is filled.

Bioresource Science

The College seeks a broadly trained scientist with experience in utilizing plants to improve the sustainable use of natural resources and improvement of environmental quality. The successful candidate is expected to develop an externally funded, interdisciplinary research program with national and international excellence in bioresource science and its application to natural resource and environmental stewardship. The candidate's academic training should be centered in plant biology, but research may focus on diverse topics such as bioenergy, bioproducts, phytoremediation, or plant genetics. Applicants should have a Ph.D. in biological sciences, with an emphasis in plant genetics, biotechnology of plants, microbiology, or biochemistry. Questions should be directed to: **Professor Linda Brubaker, Chair, Bioresource Science Faculty Search Committee: (206) 543-5778** or **lbru@u.washington.edu**. Review of applications will begin **January 31, 2006** and continue until the position is filled.

Natural Resource Informatics

A related faculty position in the College seeks applications for a nine month assistant or associate professor in the Precision Forestry Cooperative. This position description is available at the website shown below.

For complete information regarding all the positions listed above, please see **http://www.cfr.washington.edu/About/jobs.htm**.

The University of Washington is an Affirmative Action, Equal Opportunity Employer dedicated to building a culturally diverse and pluralistic faculty and staff committed to teaching and working in a multicultural environment and strongly encourages applications from women, minorities, individuals with disabilities and covered veterans.

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Tenure Track Assistant Professorships in Biological Engineering and Biotechnology

The Institute for Bioengineering of EPFL seeks **two tenure track assistant professors** in the broad fields of Biological Engineering and Biotechnology. The Institute is housed within the School of Life Sciences of EPFL and enjoys close links to the other domains of EPFL, including chemistry, engineering and materials science. Interactions with a clinical environment are possible through collaboration with the Centre Hospitalier Universitaire Vaudois and the School of Biology and Medicine of the University of Lausanne.

The open faculty positions are offered in an environment of both theoretical and experimental research, rich for both seeking deeper understanding of integrative (patho)physiological mechanisms and developing novel biotherapeutic approaches at the levels of the gene, the biomolecule, and the cell. Although the search is quite broad, the Institute seeks to grow particularly at the interface of engineering with biology, chemical biology, or computational biology.

Successful candidates are expected to initiate independent, creative research programs and participate in undergraduate and graduate teaching. We offer internationally competitive salaries, start-up resources and benefits.

Applications should include a curriculum vitae with a list of publications, a concise statement of research and teaching interests, and the names and addresses (including e-mail) of at least five professional references. Applications should reach the address below (preferably by e-mail with the files attached as PDFs) by **March 1st, 2006** at the latest:

Professor Jeffrey A. Hubbell
Head of the Search Committee
EPFL-Institute for Bioengineering (IBI), Station 15
CH-1015 Lausanne, Switzerland
E-mail: ibi@epfl.ch

For additional information on EPFL and the Institute for Bioengineering, please consult: http://www.epfl.ch and http://ibi.epfl.ch

EPFL is an equal opportunity employer

Executive Director

for the newly formed

International Neuroinformatics Coordinating Facility (INCF)

INCF is a new independent international organization created through the Global Science Forum of OECD. The INCF is currently composed of ten independent countries, who will collaborate to establish a global neuroinformatics network. This network will collect and manage neuroscientific data, and develop the database methods, tools, and modelling techniques required to facilitate access to knowledge. Each of the member countries will establish their own national neuroinformatics node, and the collective activities of these nodes will be coordinated by a Secretariat located in Stockholm at the Karolinska Institute. The Secretariat will have a staff of about 10 persons, led by an Executive Director, and two deputy directors.

The Executive Director will have a key role in the establishment and successful operation of the INCF. The Director is expected to have a solid background in neuroscience and neuroinformatics, the competence of a full professor, and be committed to the demanding task of building up the global neuroinformatics facility and coordinating this international effort aimed at cooperative integration of neuroscience information. Outstanding organizational and interpersonal skills will be required to build up this facility that will become a very important resource for neuroscience worldwide. The salary level will be subject to negotiation up to 20% above that of a full professor in Sweden.

The application should contain a CV, a list of publications, a declaration of why the candidate is interested in this position, and a brief proposal of how the candidate would approach this task. The application should be submitted to the chairman of INCF, Professor Sten Grillner. The review of the applications will commence on February 15th, 2006.

For information contact: Professor Sten Grillner.
E-mail: **sten.grillner@ki.se** Tel. +46-8-52486900

Application should be submitted to: Professor Sten Grillner, INCF and Nobel Institute for Neurophysiology, Dep. of Neuroscience, Karolinska Institutet, Retzius väg 8, SE-171 77 Stockholm, Sweden.

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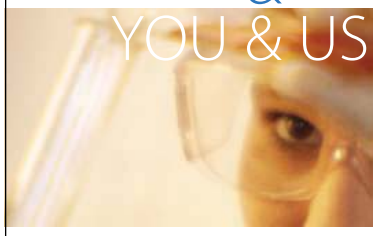

PGRD
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Imagine a career that touches the lives of people everywhere. Imagine an opportunity to reach beyond your area of expertise to make an impact on something greater than the bottom line. Imagine playing a key role in some of the most critical issues facing health care today. This is your career at Pfizer—a career unlike any other. Our **Ann Arbor, MI** facility is seeking:

Senior Scientist
Structural Biology
(X-ray Crystallography)

Join our expert crystallographers and work on the production of protein/ligand crystal structures. You'll need a PhD in Biochemistry or related field and 1-3 yrs post-doc experience solving crystal structures and familiarity with techniques of protein purification, crystallization and cryo-protection. **Req # 50543**

Senior Associate Scientist
Structural Biology
(Protein Crystallization)

You'll support structural biology for structure-based drug design by assisting with the purification and crystallization of proteins. A Bachelor's in Biology or Biochemistry along with some experience that preferably includes cloning and expression of recombinant proteins is desirable. **Req # 49752**

Senior Scientist
Structural Biology
(Protein Biophysics)

You'll play an essential role in this department as you investigate protein/ligand interactions and confirm target binding of NMR and HTS hits. Our ideal candidate holds a PhD or BS/MS with 3+ yrs experience in protein biophysics. Experience in the investigation and characterization of proteins using various techniques is a must. **Req # 49753**

Principal Scientist
Inflammation Biology

Use your expertise to develop and implement strategies for the identification and evaluation of therapeutic agents for the treatment of chronic inflammatory pain. We require that you hold a PhD with at least 3 yrs post-doc experience in pain research that includes the development of in vivo pain models. **Req # 50401**

Senior Associate Scientist
Inflammation Biology

You'll work with a multi-disciplinary group to develop novel therapies that modify disease progression and/or treat the symptoms of arthritis. You should possess a Bachelor's degree in a Biologic Science with 5 yrs research experience that includes conducting studies with laboratory animals. **Req # 50402**

We offer competitive compensation, full benefits and talented professional colleagues… some of the best and brightest in the research field today. Please apply on-line at: **www.pfizer.com/careers** and **search by requisition number**.

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Princeton Seeks Leader to Spearhead Engineering and Life Sciences Initiative

Princeton University seeks applications for a tenured faculty opening that we view as a "transformative hire" to lead a major initiative in engineering and the life sciences. The ideal candidate will be an established research leader who has an outstanding scholarly record comprising interdisciplinary efforts that link engineering, biology, and related areas.

More than half the faculty in Princeton's engineering school, including some of its most renowned researchers, work at the intersection of engineering and the life sciences. Existing strengths include biomolecular engineering, bioinformatics, robotic biomimicry, biomaterials, and ecosystem biocomplexity. In addition, leading faculty in Princeton's life sciences departments have active collaborations with engineering faculty. Building on and expanding ongoing research activities in engineering and the life sciences is a central thrust of Princeton's strategic vision, and we plan to establish new focus areas for significant growth. The successful candidate will play a major role in defining this initiative, setting its research agenda and outlining its required resources. The overall goal is to leverage considerable university resources into the development of a truly world-leading research thrust for engineering and the life sciences. The effort will involve new faculty appointments and state-of-the-art research spaces. In addition to individual achievements, the successful candidate will possess outstanding leadership skills and a sharp vision for establishing a major university effort in this area.

About Princeton University: As a research university, Princeton seeks to achieve the highest levels of distinction in the discovery and transmission of knowledge and understanding, and in the education of undergraduate and graduate students. More than 700 faculty members, who are leaders in their respective disciplines, instruct Princeton's 4,600 undergraduate students and 2,000 graduate students. The town of Princeton, NJ includes a population of roughly 30,000 people with outstanding schools and excellent neighborhoods. The central New Jersey area is well-suited for dual-career couples, with numerous large companies nearby, and within commuting distance of New York and Philadelphia.

Candidates should submit a curriculum vitae and a statement of research and teaching interests to **cels-fac-search@princeton.edu** or to: **Engineering and Life Sciences search committee, c/o Dr. Victoria Dorman, School of Engineering and Applied Science, Engineering Quadrangle, Princeton University, Princeton, NJ 08544**. Questions can be directed to **cels-fac-search@princeton.edu**. The committee will begin reviewing applications on **January 1, 2006**. For information about applying to Princeton and how to self identify, please link to **http://web.princeton.edu/sites/dof/ApplicantsInfo.htm**.

st. john's UNIVERSITY

Molecular Physiologist
Tenure Track
Department of Biological Services

St. John's University is one of the nation's largest Catholic Universities with nearly 20,000 students and five locations, four in the New York metropolitan area. At St. John's, education is not only about career preparation, but also about learning to make a difference in the world. If you share our sense of mission, we currently have the following position available in the Department of Biological Sciences.

In this tenure track position at the level of assistant or associate professor, the successful applicant will have the ability to teach in the organ-system component of our introductory biology course, offer a graduate level course in their specialty, and develop a funded research program. Outstanding candidates with research specialities in other areas of biology will be considered.

We offer competitive compensation, excellent benefits, and talented professional colleagues. For consideration, please send applications, including curriculum vitae, research and teaching plans and three letters of recommendation to: **Dr. Jay A. Zimmerman, Chair, Department of Biological Sciences, St. John's University, 8000 Utopia Parkway, Queens, NY 11439, or email them to zimmermj@stjohns.edu.**

St. John's University is an Equal Opportunity Employer and encourages applications from women and minorities.

www.stjohns.edu

QUEENS STATEN ISLAND ROME
OAKDALE LONG ISLAND MANHATTAN

Director of Microbiology Research

Affymetrix, the source for molecular technologies to understand and improve life, invented the world's first microarray in 1989 and began selling the first commercial microarray in 1994. We currently have a great opportunity in our Santa Clara, CA headquarters for a highly talented scientist with outstanding leadership capabilities to direct the scientific and technologic elements of a microbiology initiative and expand the use of Affymetrix technology for infectious disease and microbial detection.

Specifically, you will work with our Microbiology Corporate Initiatives to develop & implement strategies that accelerate growth & improvements in the human condition; define/implement a project portfolio that demonstrates the feasibility of Affymetrix technology in biodefense, public health, microbial ecology, and other applications involving microbes; and build external scientific relationships that foster a broad adoption of the technology in the relevant communities. Requires a Ph.D. in Microbiology, Molecular Biology, Biochemistry, or a related field; 5+ years of hands-on lab experience in bacteriology, virology or related fields; a record of scientific and technical innovation; expertise in molecular biology techniques such as nucleic acid sample preparation, amplification, labeling, hybridization, and data acquisition; and a keen understanding of the scientific needs of infectious disease and biodefense research communities. Experience with nucleic acid-based assay methods development and optimization on such systems is preferred, as is knowledge of microarray-based nucleic acid assay system, especially the Affymetrix GeneChip microarray system.

Email your resume to: **connie_vanlieu@affymetrix.com**. No calls or drop-ins. To learn more about Affymetrix & other opportunities and to apply online, visit our website at: **www.affymetrix.com**. *EOE*

The Way Ahead™

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Research Director
Department of Pathology
Cancer Biology
Tumor Immunology

The Department of Pathology at the University of Arkansas for Medical Sciences (UAMS) invites applications from outstanding scientists (Ph.D., M.D./Ph.D. or M.D.) for the position of Director of Research and head of the Division of Experimental Pathology. The Director will be responsible for the expansion, development and promotion of the division including aggressive recruitment of new research faculty. The successful applicant is expected to have a funded research program compatible with existing departmental strengths in cancer biology and tumor immunology. (For information on UAMS cancer-related research see: **http://www.acrc.uams.edu/cancer_research/**). The UAMS campus has experienced remarkable growth over the last decade and offers a modern and highly collaborative environment. Current extramural funding exceeds $100M annually. Nationally competitive salary and start-up packages along with state-of-the-art research laboratories are available.

Candidates should send curriculum vitae, statement of research interests and names/addresses of three references to: **Bruce Smoller, M.D., Chair, Department of Pathology, University of Arkansas for Medical Sciences, 4301 West Markham St., #517, Little Rock, AR 72205. E-mail:smollerbrucer@uams.edu**.

UAMS is an Equal Opportunity Employer, promoting workplace diversity.

University of Heidelberg

The **Faculty of Clinical Medicine Mannheim, University of Heidelberg** offers the position of an

Associate Professor (W 3) Franz-Volhard Endowed Professorship of Microvascular Biology and Pathobiology

The successful candidate should have a distinguished record of qualifications in all areas of microvascular biology and pathobiology. He/she will be appointed Head of the Section of Microvascular Biology and Pathobiology within the Research Division of Vascular Biology and Physiology at the Mannheim Center of Biomedicine and Medical Technology (MCBT). Within the Research Division, the section will closely cooperate with the W3-Aventis Foundation Endowed Chair of Vascular Biology and Tumor Angiogenesis that is jointly associated with the Faculty of Clinical Medicine Mannheim and the German Cancer Research Center (DKFZ) in Heidelberg.

As an independent principle investigator, the candidate will have special responsibility for enforcing the research mission of the Faculty with a focus on basic sciences, i.e. molecular and developmental biology, protein biochemistry, cellular biology and immunology of vascular differentiation and functions under physiological and pathological conditions. He/she is expected to actively take part in established and developing research programs of the Faculty in the field of vascular biology such as the European Graduate School "Vascular Medicine" (EU-GRK880) and the Cooperative Transregio Research Grant "Vascular Differentiation and Remodeling" (SFB/TRR23). He/she is furthermore expected to secure extramural funding by grant applications to non-university institutions. Regarding teaching duties, the candidate is expected to participate in the MD curriculum in the area of physiology/pathophysiology of vascular disease.

The successful candidate should have high ranking, internationally acknowledged academic qualifications commensurate with the rank of an associate professor including a PhD or MD/PhD, a distinguished record of original research, mentoring and teaching skills, administrative experience and an understanding of departmental financing in universities. The candidate should be a cooperative personality who will actively master the integrative task of strengthening the successful collaboration within and outside the faculty.

The position is initially available for 5 years. After successful evaluation after 5 years and given continued sponsoring for another 5 years, the position will be available unlimited. In case that the successful candidate has not been appointed to a professorship position before, State law regulation demands under chapter 50 of the University law to fill the position as a tenure track position in any case. Exceptions are possible for candidates from abroad or from non-university institutions if they cannot be attracted otherwise. When the position is to be tenured after the first 5 year turn, the formal application process need not be repeated.

The University of Heidelberg is an Equal Opportunity/Affirmative Action Employer.

Interested candidates should submit a full CV with copies of certificates, publication list and selected reprints within 4 weeks of publication of this advertisement to **Prof. Dr. Dr. h.c. K. van Ackern, Dean of the Faculty of Clinical Medicine Mannheim, University of Heidelberg, University Medical Center Mannheim, D-68135 Mannheim, Germany.**

Ten Positions in Geosciences

Institut de Physique du Globe de Paris (IPGP)

IPGP is one of the leading institutions in the world dedicated to research and higher education in the Earth and planetary sciences. It has fifteen research groups and three networks of observatories (GEOSCOPE - seismological, volcanological and magnetic). With over 450 scientists, post-doctoral fellows and Ph.D. students, IPGP enjoys the status of an independent, graduate-only university, and has a close partnership with Université Paris 7 (Denis Diderot). It has seven M. Sc. programs and awards degrees (M. Sc. and Ph.D.). It is mainly funded by the Ministry in charge of Higher Education and Research and Centre National de la Recherche Scientifique.

IPGP, Université Paris 7 and CNRS are opening 10 junior (assistant professor level) and senior (associate professor level) positions in the Geosciences in early 2006, with an effective starting date of September 1st, 2006. IPGP and Université Paris 7 advertise jointly and coordinate these new positions in the geosciences, which are opened without any condition of nationality. IPGP, Université Paris 7 (Department of Sciences of the Earth, Environment and Planets - UFR STEP) and CNRS are seeking candidates with the highest international level and potential. The following positions are advertised:

1) A professor at IPGP (associate professor level) in applied geophysics, either controlled-source seismology (seismic data processing, seismic refraction and reflection) or geo-electrical methods.

2) A professor at IPGP (associate professor level) in geodynamics of the solid Earth and planets.

3) A professor at Université Paris 7 (associate professor level) in the general fields of geochemistry and cosmochemistry.

4) A professor at Université Paris 7 (associate professor level) in experimental physics applied to the Earth (observation of natural geophysical phenomena, field and laboratory models, scaling).

5) A lecturer at Université Paris 7 ("maître de conférences", i.e. assistant professor level) in petrology (to be associated with another field of research developed in one of the IPGP research teams).

These 5 positions will be officially advertised in February by the Ministry in charge of Higher Education. They require that candidates be first "qualified" ("qualifié") by a national commission.

6) Up to three research scientists at IPGP ("chargés de recherches", assistant professor level). The fields in which the institute would like to recruit are: Seismotectonics, Biomagnetism, Physico-chemical transfer in heterogeneous porous media, Modeling of hydrothermal circulation, Integration of surface and satellite magnetic data, Early Earth and comparative planetology, Geosciences of early continents.

7) Up to three "physicien-adjoint" at IPGP (observatory position, assistant professor level). Successful candidates will be expected to accept a first assignment at one of the IPGP observatories, including those in Réunion, Martinique and Guadeloupe. The observatory assignments include support of the Geoscope global broadband seismological network, geochemistry of degassing in volcanoes, differential imaging (optical and radar) of active volcanoes and faults, volcanic seismology, and planetary instrumentation. The research majors should preferably be connected but can to some extent be independent. Positions will officially be advertised in February by the Ministry in charge of Higher Education.

Note: Listed above are conventional professor positions (research and teaching) with either IPGP or Université Paris 7 (recruited by a IPGP or Université Paris 7 committee), CNRS positions (mostly research, some teaching; fields of expertise and names are put forward by IPGP, selection is by a national committee outside IPGP and Université Paris 7), and specific positions partly dedicated to geophysical observatories (physicien-adjoint, mostly research and observatory practice, some teaching; fields of expertise and names are put forward by IPGP, selection is by a national committee outside IPGP and Université Paris 7).

Candidates for junior positions should hold a Ph.D. degree with post-doctoral experience. Candidates for senior positions should have a proven record of research and should be leaders in their fields. All candidates should send a letter of intent and a CV, and three names of scientists who could write recommendation letters, to The Director, IPGP, c/o **zerbib@ipgp.jussieu.fr.** For any further information on the positions, the research teams and observatories, the dates of publication of the positions and relevant deadlines, please consult the IPGP website (**http://www.ipgp.jussieu.fr**) or send a mail to **zerbib@ipgp.jussieu.fr** with "application to IPGP position" in the header of the message.

Institut de Physique du Globe de Paris, 4, place Jussieu - Case 89 - 75252 Paris cedex 05. Phone : +33 (0)1 44 27 24 30, Fax: +33 (0)1 44 27 33 73, Mail : zerbib@ipgp.jussieu.fr

Department Head – Department of Zoology

The Department of Zoology at Oklahoma State University (OSU) invites applications for the position of Department Head. The department is reorganizing to increase our national prominence in two research areas: (1) Ecology and Evolutionary Biology and (2) Environmental Stress. We seek a dynamic and visionary person to lead us in this endeavor. The starting date will be on or after August 2006 and is flexible.

The ideal candidate will have the academic rank of Professor, a nationally recognized research program consistent with our research foci, demonstrated success in obtaining extramural grant support, significant administrative experience, a commitment to supporting innovative teaching, and a vision for curricular reform that will produce students highly qualified for careers in research, teaching, and other professional positions.

OSU is a land-grant institution with 24,000 students located in north-central Oklahoma, 70 miles from Oklahoma City and Tulsa. Currently, the Department of Zoology has approximately 400 undergraduate and 50 graduate students, 4 staff, and 20 collegial and unified faculty with a long history of democratic governance.

Applicants should submit a letter of application, statements of research, teaching, and administrative philosophies, a curriculum vitae, and four letters of reference testifying to the applicant's leadership and administrative skills to: **Dr. Robert V. Miller, Chair, Department Head Search Committee, Department of Zoology, 430 LSW, Oklahoma State University, Stillwater, OK 74078-3052. Telephone: 405/744-6243; E-mail: bob.miller@okstate.edu**. Informal inquiries to **Dean Peter M. A. Sherwood** of the College of Arts and Sciences are welcome (Telephone: **405/744-5663**; email: **peter.sherwood@okstate.edu**). Application review will begin **1 February 2006** and will continue until the position is filled. For further information about the position, Department, and OSU, please see **http://zoology.okstate.edu**.

Oklahoma State University encourages applications from qualified women, minorities, and persons with disabilities.

Vascular Biology Center — *Pulmonary & Critical Care Medicine*

The Medical College of Georgia Vascular Biology Center and the Department of Medicine, Division of Pulmonary and Critical Care Medicine, are jointly recruiting a Pulmonary Vascular Physician-Scientist at the Assistant Professor level, tenure-track. The successful candidate will devote 85% of his/her time in research. He/she must have an earned M.D. or M.D./Ph.D. degrees and be board eligible/certified in Pulmonary and/or Critical Care Medicine. Clinical activities will be confined to 15% effort on the pulmonary consult service or in the intensive care units. The candidate will join an active group of extramurally funded vascular biologists (currently about $10 million annually, see: **http://www.mcg.edu/centers/VBC/index.html**) and pulmonary clinicians (see: **http://www.mcg.edu/som/medicine/Pulmonary/**) in recently renovated laboratories utilizing state of the art equipment. He/she will have the opportunity to participate in the two institutional pre- and post-doctoral training programs in Integrative Cardiovascular Biology. Ample opportunities for collaborative basic and clinical research are available and encouraged. The candidate is expected to develop an active, extramurally funded research program in pulmonary vascular disease. Highly competitive salary and start-up package, based on prior research experience, will be provided.

Applications should include detailed CV, statement of career goals and three letters of references and e-mailed to **John D. Catravas, Ph.D.** / **W. Bruce Davis, M.D.** at **kmartin@mcg.edu**.

The Medical College of Georgia is an AA/EOE.
Applications from women and under-represented minorities are particularly encouraged.

NANYANG TECHNOLOGICAL UNIVERSITY — NUS National University of Singapore

LEE KUAN YEW POSTDOCTORAL FELLOWSHIP

Applications are invited from young and outstanding academics for the prestigious Lee Kuan Yew Postdoctoral Fellowship (LKY PDF) in the National University of Singapore (NUS) and Nanyang Technological University (NTU).

The Fellowship is tenable for up to 3 years, with possible extension for 2 further years. LKY PDFs can apply for academic positions following the Fellowship.

Gross annual salary ranges from **S$72,000** to **S$144,000** (approx US$42,600– US$85,200) with commencing salary depending on qualifications and experience. Leave and medical benefits will be provided. For details of other benefits offered and application procedure, please visit the websites of the respective University.*

APPLICATION

Interested candidates should send their complete application package, comprising all documents listed below, to the respective University.*

- NTU Application **or** NUS Personal Particulars Form (downloadable from website).
- Detailed Curriculum Vitae, List of Publications & Educational Certificates.
- 3 International Referee Reports (including contact details).
- Statement of Research Intent (details of proposed research plan).

Closing date: 20 February 2006
Successful candidates will be notified in June 2006

* For application and contact details, please see:
NUS: http://www.nus.edu.sg/ore/funding/fellow/lky_pdf.htm
NTU: http://www.ntu.edu.sg/hr/adminres/staffrec/adlky2006.html

Edward Teller Chair of Applied Science
Department of Applied Science
University of California at Davis

The Department of Applied Science at the University of California, Davis, invites applications from, and nominations of, outstanding individuals as candidates for the Edward Teller Chair of Applied Science.

The department is seeking a senior distinguished scholar with an outstanding record in physical or applied science and a strong commitment to the education and teaching mission of the department. Apart from two undergraduate majors, Optical Science and Engineering and Computational Applied Science, the department has a strong diverse graduate program in applied physics, computational science, optics and lasers, plasma physics, biophysics, and materials science, reflecting the academic backgrounds of the faculty. The graduate program has traditionally interacted closely with the University of California managed National Laboratories, particularly the Lawrence Livermore and Lawrence Berkeley National Laboratories.

The position is open until filled. For full consideration, applications should be received on or before **February 1, 2006**. Applications, nominations, and inquiries should be directed to: **Prof. Ann Orel, Chair of the Edward Teller Chair Search Committee, Department of Applied Science, University of California, One Shields Avenue, Davis, CA 95616, U.S.A**. A complete application consists of a Curriculum Vitae with a list of at least 5 professional references and a statement of research interests and goals. Applicants must hold a PhD degree to be considered for this position. The Department is interested in candidates who have experience working with students from diverse backgrounds and a demonstrated commitment to improving access to higher education for disadvantaged students.

The University of California is an Affirmative Action/ Equal Opportunity Employer.

FACULTY POSITION IN AGING AND CANCER RESEARCH

The Department of Interdisciplinary Oncology in the College of Medicine at the University of South Florida and the H. Lee Moffitt Cancer Center & Research Institute are seeking a researcher at the Assistant/Associate/Full Professor level whose primary interests are in aging and cancer. A MD or PhD is required. MD applicants must be Florida licensed or eligible. The successful candidate will have a record of accomplishments and history of peer-reviewed funding that relates to one or more of the following themes in aging and cancer research: biology of aging, treatment efficacy and tolerance, effects of comorbidities, psychosocial issues and late effects, or palliative care and pain relief. Opportunities to conduct aging and cancer research at Moffitt are facilitated by the Center's Planning and Development (P20) Grant from NCI and NIA that supports the development of research in this area, and the Senior Adult Oncology Program that provides interdisciplinary geriatric oncology care.

Academic rank beyond that of Assistant Professor will be commensurate with experience and scholarly activity. Appointment rank at the level of Associate/Full Professor requires a minimum of five years experience at the Assistant/Associate Professor level. The position is tenure earning and salary is negotiable.

The Moffitt Cancer Center's sole mission is to contribute to the prevention and cure of cancer. The Moffitt campus includes a 162-bed cancer hospital, a Clinic with more than 130,000 patient visits per year, and active Cancer Screening facility, 250,000 sq ft of research space and a collegial, collaborative approach to translational research. Additional information is available at http://moffitt.usf.edu

The University of South Florida is a metropolitan-based Research I University enrolling more than 42,000 students. There are many opportunities for collaborative research through USF's Collaborative on Aging, a university-wide consortium of faculty who focus on the study of aging. Programs focusing on aging include the School of Aging Studies, the Center of Excellence for Aging and Brain Repair, the Alzheimer's Disease Research Center, and the Center for Hospice, Palliative Care, and End-of-Life Studies. Additional information about USF's aging programs is available at http://aging.cas.usf.edu

Please reference position no. DIO0528. Send current curriculum vitae to, S. Clifford Schold, Jr., M.D., Professor & Chair, c/o Kathy Jordan, MBA, Faculty Recruitment Specialist, Department of Interdisciplinary Oncology, 12902 Magnolia Drive, Tampa, FL 33612. Inquiries about the position can be addressed to the search chair, Paul Jacobsen, Ph.D. (jacobsen@moffitt.usf.edu). Position is open until filled. Application review begins January 16, 2006.

H. LEE MOFFITT Cancer Center & Research Institute

The End Of Cancer Begins Here.

A National Cancer Institute Comprehensive Cancer Center At the University of South Florida

USF University of South Florida College of Medicine

The University of South Florida is an EO/EA/AA institution. For disability accommodations, contact Kathy Jordan at (813) 745-1451, a minimum of five working days in advance. According to FL law, search records, including applications and search committee meetings, are open to the public.

www.moffitt.usf.edu

Vice Provost for Research and Graduate Education and Dean of the Graduate School

The University of Connecticut Storrs, CT

The University of Connecticut (www.uconn.edu), the highest-ranked public university in New England and one of the nation's premier research-extensive public universities, is in the midst of an unprecedented $2.3 billion program to enhance and expand our infrastructure. We have tripled our research funding over the last five years, while competing with other Research I institutions for the best faculty and students. With a rapidly growing research and education environment as a backdrop, we invite applications for the position of Vice Provost for Research and Graduate Education and Dean of the Graduate School.

As Vice Provost, the individual will provide visionary leadership in charting the research mission of the University and in enhancing the environment to enable the faculty to achieve that mission. Continuing to build on our exceptional record of externally funded research and training, the individual will lead the development of major university research thrusts in existing and emerging areas, and in the identification and cultivation of major research funding sources. He or she will oversee the activities and budgets of the Office for Sponsored Programs, the Graduate School, and some interdisciplinary research centers and institutes. As a member of the Provost's administrative team, the individual will advise on major policy issues affecting the University, provide leadership on policies concerning graduate education and applied and basic research, and will serve as a major advocate for the University's research to constituencies, both within and outside of the University. Technology transfer policy and other University interactions with industry and government will be coordinated by this individual, with the goal of effectively forwarding the economic development goals of the State of Connecticut.

As Dean of the Graduate School, the individual will be a member of the University's Council of Deans, chair the Executive Committee of the Graduate Faculty Council, and be directly responsible for the administration and maintenance of standards of all post-baccalaureate education and research programs at the Storrs and regional campuses of the University.

The ideal candidate will bring an appreciation for a wide range of philosophical and programmatic approaches to scientific and scholarly inquiry, academic qualifications and achievements appropriate to the position, and demonstrated ability to support interdisciplinary research, as well as research into issues of race, ethnicity, culture, gender and international affairs.

Qualifications: Candidates must possess a doctoral degree and a distinguished record of research accomplishment appropriate to qualification at the rank of Professor with tenure in an academic department of the University. Candidates should also be able to demonstrate a proven record of leadership in administrative management, budgetary responsibility, understanding of regulatory and compliance issues and coordination of interdisciplinary activities. The successful applicant will not only offer exceptional academic qualifications and leadership skills, but will also possess a personality and demeanor that is positive and collegial.

The University is located in picturesque northeastern Connecticut with convenient access to Boston and New York.

The tentative start date is July 1, 2006, and applications will be considered until the position is filled. We strongly encourage individuals from underrepresented groups, including minorities, women, and people with disabilities, to apply.

Please submit a letter of application and curriculum vitae, in both electronic and hard copy form, to:

Robert L. McCarthy, Chair, VPRGE Search Committee
c/o School of Pharmacy Dean's Office
69 North Eagleville Road, Unit 3092
Storrs, CT 06269-3092
Search # 06A170
vprgesearch@uconn.edu

The University of Connecticut is an Affirmative Action/Equal Opportunity Employer.

University of Connecticut

TEXAS STATE

PLANT BIOLOGIST TENURE-TRACK

Texas State University's Department of Biology seeks a plant biologist at the assistant professor level. An earned Ph.D. is required, and a research program involving field and molecular techniques applied to the conservation and management of plant populations, a record of extramural funding, and postdoctoral research and teaching experience are preferred. Salary and start-up packages are competitive

To apply, submit by mail a statement of teaching and research interests, curriculum vitae, unofficial transcripts, copies of up to four published papers, and contact information for four references to: **Dr. David E. Lemke, Chair, Plant Biologist Search Committee, Department of Biology, Texas State University-San Marcos, San Marcos, TX 78666**. Review of applications begins on **March 1, 2006** and will continue until a suitable candidate is identified. Visit **http://www.bio.txstate.edu** for a full description of the position and the Department's programs and faculty.

Texas State is an Equal Opportunity Employer and is committed to increasing diversity in faculty and administrative positions

VCU

Virginia Commonwealth University

TENURE-TRACK FACULTY POSITION

Chemical and Life Science Engineering

The Department of Chemical and Life Science Engineering (CLSE) in the School of Engineering at Virginia Commonwealth University (VCU) has a tenure-track faculty opening starting in the Fall of 2006. Chemical and Life Science Engineering at VCU represents the broad, formal interaction of the disciplines of chemical engineering with life and health sciences to create a forward-looking, nationally distinct program. Many of the Life Science areas at VCU enjoy national rankings, including those in the medical sciences, biological sciences and environmental life sciences.

The new School of Engineering formed in 1996 has embarked on a "25 in 25" initiative to become a top 25 program in 25 years. Notable facilities include the new 120,000 sq ft School of Engineering building, the new Trani Center for Life Sciences, the Rice Institute for Environmental Life Sciences located along the coastal plain region of the James River, and VCU's Medical School and Hospitals. Current research areas in CLSE include stem cell and stem-cell derived tissue engineering, cellular engineering and signal pathway analysis, biological systems engineering, bioinformatics and biocomputing, genetic and protein molecular engineering, small molecule and cellular based therapeutics, reaction engineering and molecular transport, advanced polymeric materials and processing methods (including medically-related polymers, supercritical solvent processing methods, and surface science). A new Institute for Life Science Engineering and a new Phase II Engineering building expansion are scheduled for ground breaking and construction over the next two years that will greatly expand and enhance research capabilities in the above areas.

Candidates should have at least one degree in Chemical Engineering or Bioengineering or closely related discipline. Outstanding candidates should submit a complete curriculum vitae, statement of research and teaching interests, and a list of four references to: **Dr. Michael H. Peters, Chair, Chemical and Life Science Engineering, Virginia Commonwealth University, 601 West Main St., Rm 403A, P.O. Box 843028, Richmond, VA 23284-3028**. Electronic submissions are acceptable by *.pdf files only please to **jbschrei@vcu.edu**. Candidates must be eligible for employment in the United States by indicating their citizenship or visa status. Review of applications will continue until the position is filled.

VCU is an Equal Opportunity/Affirmative Action Employer.
Women, minorities and persons with disabilities are encouraged to apply.

POSTDOCTORAL POSITION

Biosciences at (LLNL) has an opening for a recently graduated PhD Biomedical Scientist to conduct protein biochemistry research for the physical characterization of novel membrane-bound proteins and the complexes they form. The project will develop novel in vitro and in vivo protein expression and purification technologies. Physical characterization of proteins will be conducted using multiple techniques such as immunoassays, Uv/Vis spectroscopy, and interaction mapping.

A recent PhD in Biology, Chemistry, Molecular Biology or related discipline is required as is knowledge of protein biochemistry, protein expression and purification. Experience devising and conducting laboratory research using standard molecular biology or biochemistry techniques and knowledge of standard laboratory equipment and ES&H safety procedures is preferred. A record of publication in reputable journals in the area of protein biochemistry is required.

LLNL offers a challenging environment and a competitive salary/benefits package. To view and apply for this job, go to http://jobs.llnl.gov, Search by job #004980. When applying and prompted please mention where you saw this ad. LLNL is operated by the University of California for the Department of Energy. We are proud to be an equal opportunity employer with a commitment to workforce diversity.

University of California
Lawrence Livermore
NATIONAL LABORATORY

http://jobs.llnl.gov

MEDICAL UNIVERSITY OF OHIO AT TOLEDO

CHAIR
Department of Medical Microbiology and Immunology

Applications are invited for the position of Professor and Chair of the Department of Medical Microbiology and Immunology. We seek an outstanding scientist with a distinguished record of extramurally funded research, demonstrated leadership ability, and a strong commitment to medical and graduate education. MUO is a state supported institution with an annual budget of over 300 million dollars, situated on an attractive 450-acre campus in the port city of Toledo: **http://www.toledo.com**. The successful candidate will lead the growth of a dynamic department that currently has 10 full-time faculty members with research interests in microbial pathogenesis, signaling mechanisms in inflammation and host immune response, macrophage response to pathogens, and replication and evolution of RNA viruses. The department occupies well-equipped laboratories in close proximity to proteomics and genomics core laboratories, a modern BSL-3 facility, a microscopy/imaging core, and AAALAC-accredited animal facilities. The educational missions of the department include teaching microbiology and immunology to medical students and mentoring graduate students in the Ph.D. programs. Additional information about the department is available at: **http://www.meduohio.edu/depts/micro/index.html**.

The new Chair will be provided with resources to foster the continued growth of the department, including new tenure-track faculty positions. Immunology has been targeted for strategic emphasis. There will be strong interest in candidates with the vision and motivation both to complement the existing strengths of the department and to stimulate new research efforts with translational implications for transplant immunology, cancer immunotherapy, inflammatory diseases or host response to infection. Applications should include: (1) a cover letter summarizing research, educational and administrative background, (2) a curriculum vitae, and (3) names and contact information for at least four references. Materials may be sent via regular mail or e-mail (PDF format) to: **William A. Maltese, Ph.D., Chair of the Microbiology Search Committee, c/o Shirley Joseph, COM Dean's Office, Medical University of Ohio, 3045 Arlington Avenue, Toledo, OH 43614; sjoseph@meduohio.edu**.

The Medical University of Ohio is committed to diversity and equal opportunity. Applications from women and minority candidates are strongly encouraged.

POSITIONS OPEN

ASSISTANT/ASSOCIATE PROFESSOR and DIRECTOR, MASTER of BIOTECHNOLOGY PROGRAM

The Department of Biological Sciences at San José State University (SJSU)seeks applicants for a tenure-track position at the level of Assistant or Associate Professor. Applicants should have a Ph.D. degree in a biotechnology-related field, and research and teaching experience. The Director will recruit and retain students for the Master of Biotechnology (MBT) Program **(website: http://www.science.sjsu.edu/mbt),** design and implement innovative biotechnology curriculum, and teach biotechnology courses. The Director will also maintain close contact with the biotechnology industry and require students in the program to obtain internships in biotechnology, and have primary responsibility for promoting the MBT program within the University, the California State University system, and the biotechnology industry locally and nationally. As a member of the regular faculty, the Director will also teach biology courses and direct student research as necessary, and be active in scholarly activities related to biotechnology. The new faculty member must address the needs of a student population diverse in age, ethnicity, and culture. For consideration, send a letter of application, curriculum vitae, official university graduate transcripts, statement of teaching and research interests, and three letters of reference to: **Master of Biotechnology Search Committee, Department of Biological Sciences, San José State University, One Washington Square, San José, CA 95192-0100.** Please include job requisition number JRN 012168 on all correspondence. Review of applications will commence on February 1, 2006, and continue until the position is filled. Visit **website: http://www.sjsu.edu/depts/Biology.** *SJSU is an Equal Opportunity/Affirmative Action Employer committed to the core values of inclusion, civility, and respect for each individual.*

ECOSYSTEM ECOLOGIST

Applications are invited to fill a tenure-track position in Kent State's Department of Biological Sciences (**website: http://www.kent.edu/biology**) at the level of **ASSISTANT PROFESSOR.** This position is part of an ongoing expansion of the faculty in biological sciences. Researchers in all areas of ecosystem ecology will be considered, but we are particularly interested in applicants who complement the strengths of our ecology program. The Department has access to a variety of field sites and superb core research facilities and offers competitive startup packages. The successful candidate is expected to establish a high-quality, extramurally funded research program and exhibit a commitment to excellence in graduate and undergraduate education. Applicants must have a Ph.D. degree and postdoctoral experience.

Applicants should send their curriculum vitae and relevant reprints, statement of research and teaching interests, and three letters of recommendation to:

Chair, Ecosystem Ecology Search Committee
Department of Biological Sciences
Kent State University
P.O. Box 5190, Kent, Ohio 44242-0001
Fax: 330-672-3713

Review of applications will begin February 2, 2006, and continue until the position is filled.

Kent State University is an Affirmative Action/Equal Opportunity Employer and encourages applications from candidates who would enhance the diversity of the University's faculty.

EUKARYOTIC MOLECULAR GENETICIST
Minnesota State University, Mankato

The Department of Biological Sciences invites applications for a tenure-track ASSISTANT PROFESSOR position beginning August 21, 2006. For complete position description and application procedures, see: **website: http://www.mnsu.edu** (link to Employment at MSU) or contact the Department of Biological Sciences at **telephone: 507-389-2786.** *Affirmative Action/Equal Opportunity Employer and a member of the Minnesota State Colleges and Universities System.*

POSITIONS OPEN

ASSISTANT or ASSOCIATE PROFESSOR in MOLECULAR GENETICS
University of Alberta
Department of Biological Sciences

The Department of Biological Sciences at the University of Alberta invites applications for a tenure-track position at the Assistant or Associate Professor level in research areas related to molecular genetics. Candidates should have a strong record of research using genetic tools to address a basic problem in molecular, cellular, and/or developmental biology. Candidates should also have the potential for excellence in teaching within our undergraduate and graduate programs in molecular genetics. The successful candidate will interact with a dynamic group of colleagues with expertise in molecular, cellular, and/or developmental genetics. Candidates must have a Ph.D. and two or more years of postdoctoral research experience.

The University of Alberta offers a competitive salary commensurate with experience and an excellent benefits plan. The Department of Biological Sciences **(website: http://www.biology.ualberta.ca/),** with 70 faculty members and 275 graduate students, offers an exciting environment for collaborative research. Exceptional infrastructure includes a microarray and proteomics facilities, molecular biology and advanced microscopy service units, and aquatic and terrestrial animal care and plant growth facilities. Candidates should submit curriculum vitae, a one-page summary of research plans, a statement of teaching interests, and reprints of their three most significant publications electronically to **e-mail: positions@biology.ualberta.ca** or by mail to:

Dr. L. S. Frost, Chair
Department of Biological Sciences
CW 405 Biological Sciences Building
University of Alberta
Edmonton, Alberta, Canada T6G 2E9

Applicants must also arrange for three confidential letters of reference to be sent to the Chair. The closing date is February 15, 2006. The effective date of employment will be on or after July 1, 2006.

All qualified candidates are encouraged to apply; however, Canadians and permanent residents will be given priority.

The University of Alberta hires on the basis of merit. We are committed to the principle of equity in employment. We welcome diversity and encourage applications from all qualified women and men, including persons with disabilities, members of visible minorities, and Aboriginal persons.

FACULTY POSITION
DEPARTMENT of PHYSIOLOGY and FUNCTIONAL GENOMICS
University of Florida College of Medicine

The Department of Physiology and Functional Genomics invites applications from outstanding individuals for a tenure-track faculty position at the Assistant-, Associate- or Full Professor levels (two positions available). Candidates must have a Ph.D. and/or M.D. degree, postdoctoral research experience in integrative/cellular/molecular physiology, and must demonstrate a good record of publications and research productivity. The successful candidate will be expected to develop a strong, extramurally supported, independent research program. Candidates will be expected to teach in medical, dental, and graduate school courses and mentor graduate students. The College of Medicine has Interdisciplinary Centers in hypertension, mammalian genetics, cancer, and gene therapy as well as the McKnight Brain Institute. Salary is commensurate with qualifications and experience. Along with a cover letter, please submit curriculum vitae, a statement of research plans, and names of at least three references to: **Chris Baylis, Ph.D., Chair, Faculty Search Committee, Department of Physiology and Functional Genomics, P.O. Box 100274, University of Florida College of Medicine, Gainesville, FL 32610-0274.** Application deadline: February 28, 2006. Anticipated start date: July 1, 2006. *The University of Florida is an Equal Opportunity Institution. Women and minorities are encouraged to apply.*

POSITIONS OPEN

DIRECTOR
Sticht Center on Aging and Rehabilitation
Wake Forest University School of Medicine

Wake Forest University School of Medicine seeks applications for the position of Director of the Sticht Center on Aging and Rehabilitation which will include a faculty appointment in the Department of Internal Medicine. Candidates should have the M.D. or Ph.D. degree, must have demonstrated excellence in research, and possess exceptional leadership qualities. The successful candidate will be charged with building on a solid foundation of aging research that emphasizes excellence in research and teaching. For M.D. candidates, opportunities exist for leadership of the Section on Gerontology and Geriatric Medicine.

The Center currently consists of five physician and five non-physician faculty members with primary appointments in the Section of Gerontology and Geriatric Medicine; however, more than 60 faculty participate in the multidisciplinary research programs of the Center on Aging. The Center offers a large program for clinicians and scientists that provides training in gerontology and geriatrics for medical students, residents, and clinical and research fellows, as well as junior faculty members. The Sticht Center on Aging has gained national and international recognition for excellence through a high level of NIH funding including a Claude D. Pepper Older Americans Independence Center, and by attracting scientists and trainees from the United States and throughout the world. The Director of the Sticht Center directly reports to **Dr. William Applegate,** Dean of the School of Medicine.

The Sticht Center on Aging is a leader in clinical care, providing innovative services to meet the special health care needs of older adults across a full range of geriatric practice settings (inpatient, outpatient, home, and long-term care) as well as rehabilitation; and psychiatric care. Applications including a current curriculum vitae or nominations should be sent by mail or e-mail to: **William Sonntag, Ph.D., Chair, Search Committee for Director of the Sticht Center, Attn: Adriene Cunningham, Dean's Office, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157. E-mail: wsonntag@wfubmc.edu.** *Affirmative Action, Equal Opportunity Employer.*

Adelphi University College of Arts and Sciences invites applications for **ASSISTANT PROFESSOR** of biology, tenure-track for fall 2006. Required: Ph.D. with strong research and teaching credentials; area of expertise open. To teach human body (anatomy and physiology) for nonmajors and biology majors; develop active research program involving undergraduates/Master's students; develop or participate in advanced courses within area of expertise. Please go to **website: http://www.adelphi.edu/dataform/,** complete Faculty Data Form and send letter of interest, curriculum vitae, three references to: **James Dooley, Adelphi University, 1 South Avenue, P.O. Box 701, Garden City, NY 11530-0701.** For complete details on this position and application process, please visit **website: http://www.adelphi.edu/positions/faculty.** Availability of position is subject to final budget approval. Appointment is subject to final approval by the Board of Trustees. For additional information about Adelphi University please visit our **website: http://www.adelphi.edu.** *Adelphi University is committed to building a diverse faculty and strongly encourages applications from minority and women candidates. Adelphi University is an Affirmative Action/Equal Opportunity Employer.*

POSITION in DEVELOPMENTAL BIOLOGY
Department of Biology
Dalhousie University

We invite applications for a full-time probationary tenure-track Assistant Professor position in developmental biology. Please see **website: http://biology.dal.ca/positions/development.html** for more details.

TEMPLE UNIVERSITY
DEPARTMENT OF CHEMISTRY
FACULTY POSITIONS

The Department of Chemistry at Temple University invites applications and nominations for two tenured/tenure-track faculty positions with an emphasis on **Organic and Biochemistry**. These positions are open with respect to rank. Applicants at the Assistant Professor level are expected to demonstrate strong potential for establishing a vigorous research program funded by peer-reviewed research grants and for developing excellence in teaching. Applicants at the Associate and Full Professor levels are expected to have established research programs of high quality, supported by substantial externally funded peer-reviewed research grants and demonstrated significant teaching accomplishments. Salaries are highly competitive and substantial resources have been provided for start-up funding. Ample modern laboratory space is available.

The Department of Chemistry (**http://www.chem.temple.edu**) is engaged in a new initiative of growth in research and education, and enjoys multiple collaborative interactions with research groups in other departments in the College of Science and Technology, the College of Engineering, and the Health Sciences campus. Temple University (**http://www.temple.edu**), located in historic Philadelphia, is part of the Pennsylvania Commonwealth System of Higher Education, and serves over 34,000 students. Philadelphia is a vibrant center of the arts and sciences and a major locus of chemical, biomedical, pharmaceutical and biotechnological research and development.

Applicants should submit a *curriculum vitae*; a statement of research interests and (if applicable) current grant support; a statement of teaching philosophy; and arrange to have four letters of recommendation sent to: **Dr. Robert J. Levis, Professor and Chair, Department of Chemistry (016-00), Temple University, Beury Hall, 13th and Norris Streets, Philadelphia, PA 19122**. Review of applications will begin immediately and will continue until suitable candidates are identified.

Temple University is an Equal Opportunity/Affirmative Action Employer. The Department specifically invites and encourages applications from women and minorities.

The Robert A. WELCH Foundation
Distinguished University Chair in Chemistry
Dept. of BIOCHEMISTRY
The University of Texas Health Science Center at San Antonio

We are seeking candidates at the Professor or senior Associate Professor level with expertise and experience in the broad areas of **Molecular, Chemical and/or Structural Investigations of Signaling Networks.** Research areas that encompass chemical or structural analysis of macromolecular complexes, cryo-EM, structure-based drug design, single molecule imaging or others relating to analysis of signal transduction networks will be considered.

As an endowed chair, the position comes with significant resources, space and a highly competitive salary. The selected candidate will be expected to play a leadership role in the on-going program of hiring within the department over the next several years. Currently, the Department has 22 primary, and 6 cross-appointed faculty whose research activities include a broad range of fields, including enzymology, signaling, transcriptional regulation, neuroscience, membrane and organelle biology and intercellular communication (http://www.biochem.uthscsa.edu/). There is a significant structural biology focus within the department that is supported by extensive state-of-the-art core facilities in X-ray, NMR, mass spec., anal. ultracentrifugation and SPR.

UTHSCSA is located northwest of downtown San Antonio in the South Texas Medical Center, gateway to the scenic Texas Hill Country, with its many recreational opportunities and boutique wineries. UTHSCSA consists of five schools, including a Medical School, Graduate School of Biomedical Sciences, Dental School, School of Nursing and School of Allied Health Sciences. San Antonio is the 9th largest city in the U.S. with a beautiful, historical downtown area featuring a riverwalk with its diverse entertainment and many fine restaurants.

Please submit a Curriculum Vitae, description of research interests, list of four referees and a cover letter to **Dr. Bruce J. Nicholson, Chair of Biochemistry, MSC 7760, UTHSCSA, 7703 Floyd Curl Dr., San Antonio, TX 78229-3900.**

The University of Texas Health Science Center at San Antonio is an Equal Employment Opportunity/Affirmative Action Employer. All faculty appointments are designated as security sensitive positions.

UNIVERSITY of CALIFORNIA
Riverside

Senior-Level Professor and Department Chair Position
Department of Biochemistry

Position Description: The Department of Biochemistry, University of California, Riverside (**http://www.biochemistry.ucr.edu/**), invites applications for Professor and Department Chair with summer salary. Appointment is to begin on or after July 1, 2006. The appointment requires evidence of nationally/internationally recognized achievements, an established record of extramurally funded research, significant research collaborations, and administrative skills. **Research:** The specific area of research is open and can include fundamental questions on topics such as (1) molecular imaging, including structural analysis of proteins, 3-D imaging of the cell's proteome, and real time imaging in living cells at a systems level; (2) molecular control of cell fate, including epigenetics, signal transduction, gene regulation, and stem cell research; (3) molecular mechanisms of aging-related diseases. The University of California at Riverside is undergoing a significant period of growth. The Chair will participate in the development of the new Health Sciences Research Institute. **Teaching:** The successful candidate will participate in training graduate students, and will contribute in teaching at the graduate and undergraduate levels. An attractive start-up package will be provided with salary commensurate with education and experience. **Requirements:** A Ph.D., M.D., or equivalent degree in biochemistry or a closely related field and the proven ability to conduct innovative research are required.

Application: Interested individuals should forward (1) a curriculum vitae, (2) a brief statement of research interests, and (3) the names and addresses (postal or email) of at least three references to: **Professor Michael F. Dunn, Chair, Search Committee, Department of Biochemistry, University of California, Riverside, CA 92521-0129**. Electronic applications are encouraged (send to **michael.dunn@ucr.edu**). Evaluation of applicants will begin **January 15, 2006**, but the position will remain open until filled. For additional information about the UCR campus, visit **http://www.cnas.ucr.edu**.

Women and members of underrepresented minority groups are especially encouraged to apply. The University of California is an Affirmative Action/Equal Opportunity Employer.

POSTDOCTORAL FELLOWSHIPS
IN CANCER RESEARCH

The University of Texas M. D. Anderson Odyssey Program encourages the newest generation of cancer researchers to explore novel areas of clinical or basic cancer research in preparation for successful, independent careers in this field while taking advantage of the resources offered by The University of Texas M. D. Anderson Cancer Center in Houston, Texas. The Odyssey Program supports the training and research efforts of dedicated scientists at the beginning of their careers by sponsoring outstanding junior and senior postdoctoral fellows who wish to pursue innovative cancer research. Odyssey Scholarships and Fellowships are awarded based on level of experience, strength of credentials, and potential of proposal. Odyssey Fellows and Scholars receive up to three years of support for their salaries and a yearly research allowance for supplies, small equipment and meeting expenses.

2005-2006 Application Deadlines:

Odyssey Fellowship:

- March 6, 2006 (notice of intent due February 6, 2006)
- October 2, 2006 (notice of intent due September 4, 2006)

Odyssey Scholarship

- No fixed deadline (notice of intent due 3 weeks prior to submitting application)

For further information, consult our website:
http://www.mdanderson.org/odyssey

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER
Making Cancer History™

M. D. Anderson Cancer Center is an Equal Opportunity Employer and does not discriminate on the basis of race, color, national origin, gender, sexual orientation, age, religion, disability or veteran status, except where such distinction is required by law. All positions at M. D. Anderson are considered security sensitive; drug screening and thorough background checks will be conducted. The University of Texas M. D. Anderson Cancer Center values diversity in its broadest sense. Diversity works at M. D. Anderson. Smoke-free environment.

POSITIONS OPEN

ASSISTANT/ASSOCIATE PROFESSOR
Medicinal Chemistry of Central Nervous System-Targeted Molecules
The University of Montana

Applications are invited for a tenure-track Faculty Position in the Department of Biomedical and Pharmaceutical Sciences to strengthen research and graduate education in the medicinal chemistry of small molecules active in the central nervous system (CNS) as part of an NIH-funded Center for Biomedical Research Excellence (COBRE) in Structural and Functional Neuroscience. Research in the Center focuses on CNS protein structure/function as related to transport, membrane protein dynamics and neuropathology. Much of the progress and growth of the Center has been linked to the successful integration of medicinal chemistry, biochemistry and physiology with the aim of developing small molecules to advance our understanding of neuronal function and CNS disease. We wish to continue this effort by recruiting a new Assistant or Associate Professor. Successful candidates will be expected to establish vigorous externally funded research programs that complement Departmental and Center strengths, supervise graduate students, and be committed to teaching excellence at the graduate and undergraduate levels. Applicants must have a doctoral degree, postdoctoral research experience, and demonstrated ability or potential to secure NIH funding. A competitive startup package is available. The University of Montana is also the recipient of a National Science Foundation Advance Award focused on increasing the presence of women in science. Applications received by February 15, 2006, will receive full consideration; review will continue until the position is filled. More detailed information may be obtained from the **Center Director, R. Bridges (e-mail: richard.bridges@umontana.edu)** or from **website: http://www.umt.edu/csfn.**

Loyola University Chicago seeks candidates for a **FULL-TIME, NON-TENURE-TRACK INSTRUCTOR POSITION** (three-year term with possibility of renewal), with dual appointment in the Department of Natural Science and the Center for Science and Mathematics Education (CSME). The Department of Natural Science serves the University Science Core for non-science majors, and the Environmental Studies/Science Program (ESP). The CSME provides outreach to improve science and math education in Chicago-area schools. Applicants must have a Ph.D. in an area of life or physical science that will enhance faculty expertise within the College in Earth, space or environmental science. The successful candidate will have a well-defined interest in teaching non-science majors. Teaching responsibilities (four sections/semester) will include courses in the science core curriculum and in either the CSME or Loyola's ESP. Loyola is an urban campus in a community rich in economic, social, and ethnic diversity, and strives to ensure that this diversity is reflected in its faculty, students, and staff. Applicants should submit curriculum vitae, three letters of recommendation, and a teaching statement to: **Chair of Search Committee, Department of Natural Science, Loyola University Chicago, 6525 N. Sheridan Road, Chicago, IL 60626.** Review of applications will begin on February 1, 2006, and continue until the position is filled. *Loyola University is an Equal Opportunity/Affirmative Action Employer and is committed to diversity in its workplace.*

ECRI, a health services research and publishing organization designated as an evidence-based practice center (EPC) by the U.S. Agency for Healthcare Research and Quality, is seeking a **CHIEF METHODOLOGIST** to oversee technical work conducted by the Health Technology Assessment Group on assessments of medical drugs, devices, and procedures, including project design and methods of analysis. Act as ECRI's primary statistical resource (including project/study design and data analysis) when requested by other ECRI groups. For details on this position, please go to Careers at ECRI on the homepage of **website: http://www.ecri.org.**

FACULTY POSITION: RESEARCH TRACK ASSISTANT, ASSOCIATE, OR FULL PROFESSOR
Northwestern University
Feinberg School of Medicine

Applications are invited for a full-time, continuing nontenure-track appointment at the rank of Research Assistant, Research Associate, or Research Professor in the Robert H. Lurie Comprehensive Cancer Center, Northwestern University (NU), Feinberg School of Medicine, Chicago. The M.D. or Ph.D. candidate will focus on bridging the gap between basic science laboratories and clinical studies. Specifically, the candidate will work with NU investigators through the Pathology Core Facility of the Robert H. Lurie Comprehensive Cancer Center (PCF) (which is a shared resource of the Cancer Center) and Eastern Cooperative Oncology Group (ECOG) investigators via the Pathology Coordinating Office and Reference Laboratory (PCO-RL) (which is the solid tumor bank and reference laboratory for ECOG) to help design translational science protocols. The candidate will have access to prospectively or retrospectively collected specimens from patients enrolled on ECOG clinical trials in breast, GI, GU, thoracic, hematopoietic (lymphoma, leukemia), and other malignancies.

The candidate will be expected to have a working knowledge of molecular techniques used in the analysis of carcinogenesis, molecular biology of cancer, cancer prognostication, and directed, cancer therapeutics. These techniques include but are not limited to tissue-based assays, DNA/RNA/protein extraction, polymerase chain reaction, fluorescent in situ hybridization, microsatellite instability, and proteomics. NU and ECOG have a wealth of human biological materials available for study from local and national, NCI-sponsored clinical trials. As such, these materials are linked to clinical outcome. The candidate will be expected to work closely with the Laboratory Science/Pathology Committee of ECOG.

Send curriculum vitae, a letter outlining your interests and strengths, and names of five references to: **Dr. Michael Pins, e-mail: m-pins@northwestern.edu.**

Northwestern University is an Equal Opportunity/Affirmative Action Employer. Women and minority candidates are encouraged to apply. Hiring is contingent upon eligibility to work in the United States.

RESEARCH SCIENTIST or RESEARCH ENGINEER
Hitachi Chemical Research Center, Inc.

Hitachi Chemical Research Center, Inc. (HCR), a subsidiary of Hitachi Chemical Company, Ltd., is located in Southern California on the University of California Irvine campus. HCR is a research and development company directed towards novel technology platforms and related biomaterials for life sciences. The candidate will focus on research in the nanotechnology or nanomaterial fields to develop polymer based functional materials. The individual will create, develop and direct his/her own project. Candidate must be an independent researcher who has demonstrated scientific creativity and technical proficiency in his/her field. In addition, the candidate must have a strong background in chemistry, preferably working with polymers or in material sciences. Position requires a minimum of a Ph.D. in science or engineering. HCR offers competitive benefits and salary. Interested candidates can e-mail resumes to **Ms. Lisa Osborn** at **e-mail: losborn@hcrcenter.com.** *Equal Opportunity Employer.*

The National Oceanic and Atmospheric Administration (NOAA), National Centers for Coastal Ocean Science (NCCOS) seeks a GS-0401-15, **ENVIRONMENTAL SCIENTIST,** to serve as the **DEPUTY DIRECTOR** of NCCOS. The position opened December 14, 2005, and closes January 18, 2006. The salary range is $103,947 to $135,136. To view a copy of the vacancy announcement and develop and submit a resume, please visit **website: https://jobs1.quickhire.com/scripts/doc.exe.** The vacancy number is NOS-CCOS-2006-0007.

ASSISTANT PROFESSOR
Microbiology

The Agnes Scott College Department of Biology is seeking applications for a tenure-track position in microbiology at the rank of Assistant Professor. Applicants must have a Ph.D. in biological sciences, a commitment to excellence in teaching, and a record of achievement in research. The successful candidate will teach an upper division course in microbiology, a portion of an introductory-level cellular and molecular biology course, a capstone seminar in microbiology, and other courses, depending on qualifications. The successful candidate is also expected to establish an active research program involving undergraduates. The Department of Biology is housed in a new Science Center with individual and shared research facilities and equipment. Agnes Scott College is affiliated with the Centers for Disease Control and Prevention through an exchange program for internships, research, and instruction. More detailed information about the Department and the College can be obtained from the **website: http://www.agnesscott.edu.**

Review of applications will begin January 30, 2006, and continue until the position is filled. Ph.D. applicants should send a cover letter, curriculum vitae, statement on teaching philosophy and experience, description of research activities/experience and future directions, and contact information for three references to: **Microbiology Search Committee Chair, Department of Biology, Agnes Scott College, 141 E. College Avenue, Decatur, GA 30030.** Electronic application submissions will not be accepted.

Agnes Scott College is a highly selective, independent national liberal arts college for women located in metropolitan Atlanta. Agnes Scott has a strong commitment to diversity and urges members of underrepresented groups to apply. Equal Opportunity Employer.

TENURE-TRACK FACULTY POSITION in Cancer Immunology

The Department of Pathology and Microbiology, School of Medicine, University of South Carolina (USC), Columbia and the South Carolina Cancer Center are undergoing major expansion. Applications are invited for a tenure-track Assistant/Associate/Full Professor position in cancer immunology. Candidates for the Assistant Professor position must have a Ph.D. or M.D. or equivalent with postdoctoral research experience. Candidates for Associate/Full Professor positions should have current extramural funding. Competitive salary and startup funds are available. Candidates are expected to develop a strong, extramurally-funded research program and participate in the teaching mission of the Department. Apply with curriculum vitae, statement of research plans, and three letters of recommendation to: **Dr. Mitzi Nagarkatti, Chair, Department of Pathology and Microbiology, University of South Carolina School of Medicine, Columbia, SC 29208.** Or **e-mail: pathmicroimads@gw.med.sc.edu.** The search will start immediately and continue till the position is filled. *USC Columbia is an Equal Opportunity/Affirmative Action Employer and encourages applications from women and minorities.*

POSTDOCTORAL FELLOW in IMMUNOLOGY at UCLA

Ph.D. or M.D. trainees with experience in cellular immunology and flow cytometry may apply to work in the area of autoimmune diseases. Please send your curriculum vitae and the e-mail addresses and telephone numbers of three references to: **Ram Singh** at **e-mail: rrsingh@mednet.ucla.edu.**

A POSTDOCTORAL RESEARCH POSITION is available at **Stevens Institute of Technology,** Hoboken, New Jersey for a candidate with a strong background in molecular biology and patch-clamp techniques to investigate the molecular mechanism of ion channel regulation in cellular trafficking. Curriculum vitae with addresses of three references should be sent to **e-mail: ssaxena@stevens.edu.**

TEXAS A&M UNIVERSITY

ASSOCIATE DEAN FOR RESEARCH AND GRADUATE STUDIES COLLEGE OF VETERINARY MEDICINE AND BIOMEDICAL SCIENCES TEXAS A&M UNIVERSITY

Position Description: The College of Veterinary Medicine at Texas A&M University invites applications and nominations for the position of Associate Dean for Research and Graduate Studies.

Qualifications: The successful candidate will be an established scientist in veterinary medical and/or biomedical research with a strong record of scholarly achievement, peer recognition and sustained extramural funding as a principal investigator. Excellent interpersonal communication skills, substantial experience in graduate education, demonstrated leadership and organizational abilities and firsthand experience with a variety of funding sources which support veterinary or biomedical research are required. A terminal doctoral degree in the biomedical sciences and academic administrative experience are required. DVM or equivalent and specialty board certifications are desirable.

Responsibilities: The Associate Dean for Research and Graduate Studies reports directly to the Dean of the College, is a member of the administrative team of the College, and is responsible for managing the administrative aspects of the research and graduate studies programs in the College. The successful candidate must have a scholarly record that merits appointment as a tenured professor in a department within the College.

Position posting date: 4 January 2006

Application review: Review of applications and nominations will begin immediately and continue until the position is filled.

Application procedure: Applicants should submit a letter of intent, curriculum vitae, and reference list. References will not be contacted until the advanced stages of screening, and candidates will receive prior notification. Inquiries, nominations, and applications should be submitted to: **Dr. Glen A. Laine, Search Committee Chair, 4466 TAMU Department of Physiology and Pharmacology, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX 77843-4466; Telephone: 979-845-7261; email: glaine@ tamu.edu**.

Texas A&M University is an Equal Opportunity Employer. Ethnic minorities and women are encouraged to apply. The candidate selected for this position must be able to meet eligibility requirements to work in the United States at the time of appointment and must be able to communicate effectively in the English language.

A description of the college and its rapidly expanding programs, along with information about our academic community, is available at **http://www.cvm.tamu.edu**.

GEORGIA CAMPUS PCOM

Assistant/Associate Professor

Georgia Campus – PCOM is seeking candidates for the following full-time faculty positions for its **Division of Basic Sciences**. The GA-PCOM teaches an integrated medical curriculum to osteopathic medical students and has an evolving graduate program in biomedical sciences; candidates for these positions will be expected to make contributions to the teaching of master's level candidates in our biomedical sciences graduate program. Candidates will be expected to engage in scholarly activity by engaging in research activities that will support graduate program development including mentoring of students, publication of works and the pursuit of extramural funding to support an independent research program. Candidates for each position must have an earned PhD degree in the respective field or closely related area; postdoctoral experience is required.

Biochemistry and Molecular Biology

Candidates must have ability to teach in the area of medical biochemistry and/or molecular biology. Emphasis will be given to candidates in the areas of molecular biology/genetics and nutritional biochemistry.

Pharmacology

Candidates will be expected to participate in the teaching of medical pharmacology to osteopathic medical students. Emphasis will be given to candidates in the area of neuro-pharmacology/neuroscience.

Anatomy

Candidates must be capable of teaching medical gross anatomy, including instruction in cadaver-based laboratory and contribute to an evolving graduate program. Preference will be given to individuals with teaching experience in neuroanatomy, histology, embryology and/or biomechanics/kinesiology.

The Georgia Campus of PCOM is Georgia's newest medical college with an enrollment of 86 students in its inaugural class. The campus is located in beautiful Suwanee, Georgia, just 38 miles from the airport and 33 miles to downtown Atlanta.

Candidates should send letter of interest and curriculum vitae to: **Philadelphia College of Osteopathic Medicine, Human Resources Department, 4190 City Avenue, Philadelphia, PA 19131, Fax 215-871-6505 or email: hr@pcom.edu** EOE

www.pcom.edu

CHAIR POSITION
Department of Pharmaceutical Sciences
Washington State University
Pullman, WA

The Department of Pharmaceutical Sciences invites applications from qualified candidates for a department chair position at the tenured full professor level to begin on or about September 1, 2006. Candidates must have a Ph.D. and/or M.D. in a biomedical discipline and an active independently funded research program. Current research strengths of the department include cancer, inflammation and pain; therefore, preference will be given to established investigators with a strong track record in biomedical disciplines that build on or complement these areas. Additionally, the successful candidate will have leadership capabilities and a commitment to sustaining and expanding the research and teaching environment at Washington State University. Demonstrated competence in the development and/or implementation of professional and graduate curricula and an excellent record of mentoring is desirable. See department webpage (URL: **http://www.pharmacy.wsu.edu/PharmSci/**) for additional information. Screening of applicants will begin **February 15, 2006**. To apply, please submit the following: a letter of application explaining how the candidate's record relates to the qualifications and responsibilities listed; a *curriculum vitae*; and the names and contact information of three professional references only. Send (e-mail acceptable) to: **Raymond M. Quock, Ph.D., Search Committee Chair, Dept. of Pharmaceutical Sciences, College of Pharmacy, P.O. Box 646534, Washington State University, Pullman, WA 99164-6534, quockr@mail.wsu.edu**.

WSU is an EO/AA Educator and Employer.

AWARDS

MDI Biological Lab

NEW INVESTIGATOR AWARDS

Applications are invited for New Investigator Awards (NIAs) at the Mount Desert Island Biological Laboratory (MDIBL) for the 2006 summer season. MDIBL is an independent marine-focused institution with research interests in the areas of marine physiology, cell biology, functional genomics, bioinformatics, toxicogenomics, developmental biology and neuroscience. Research projects should use marine organisms available at MDIBL. NIA funding covers lab rental, housing, and user fees. Funding is provided by the Maren Foundation, MDIBL sources, and the NIEHS supported MDIBL Center for Membrane Toxicity Studies. The length of any appointment is flexible; most investigators spend 1-4 months.

Application forms (to be returned no later than **February 15, 2006**) and details on resources at MDIBL are available from **http://www.mdibl.org/docs/index.shtml** and **http://www.mdibl.org/research/index.shtml**.

POSITIONS OPEN

ASSISTANT PROFESSOR DEVELOPMENTAL BIOLOGIST

The Department of Biological Science at the University of Tulsa seeks a tenure-track Assistant Professor with expertise in developmental biology, preferably with an organismal perspective focusing on evolutionary/developmental biology. The successful candidate will develop an independent, extramurally funded research program and train graduate and teach undergraduate students. A Ph.D. degree and postdoctoral experience are required. The position begins 15 August 2006.

The University of Tulsa is a private, comprehensive university with a strong commitment to research and teaching. The Department of Biological Science has a faculty of 14 and offers B.S., M.S., and Ph.D. degrees. The Department has excellent research facilities and supporting core labs for DNA sequencing, confocal microscopy, and microarray analysis. Review of applications will begin 1 February 2006. To apply, send curriculum vitae, statement of research and teaching interests, reprints, and three letters of reference to: **Search Committee Chair, Department of Biological Science, The University of Tulsa, 600 South College Avenue, Tulsa, OK 74104.**

The University of Tulsa is an Equal Opportunity/Affirmative Action Employer.

ASSISTANT/ASSOCIATE PROFESSOR PHYSIOLOGIST, TENURE-TRACK

The Department of Comparative Biomedical Sciences is seeking a Physiologist at the rank of tenure-track Assistant/Associate Professor. Applicants must be capable of teaching at least two organ systems in comparative vertebrate physiology. Required qualifications: Ph.D. or equivalent degree in physiology and/or biological/biomedical sciences. Additional qualifications desired: D.V.M. degree; postdoctoral experience. Primary responsibilities include: teaches in a two-semester, team-taught, physiology course in the veterinary professional curriculum; establishes a competitive, extramurally funded research program. The Department has numerous well-funded investigators in cell and molecular biology. Salary and rank will be commensurate with qualifications. Application deadline is February 15, 2006, or until candidate is selected. An offer of employment is contingent on a satisfactory pre-employment background check. Submit letter of application and resume (including e-mail address) to: **Dr. William G. Henk, Professor, Comparative Biomedical Sciences, School of Veterinary Medicine, Louisiana State University, Reference 000097, Baton Rouge, LA 70803. Telephone: 225-578-9898; e-mail: henk@vetmed.lsu.edu.**

LSU is an Equal Opportunity/Equal Access Employer.

TWO POSTDOCTORAL POSITIONS are available immediately. The first position will study the mechanisms of the in vivo role of Quinone Oxidoreductases (NQO1 and NQO2) in regulation of tumor suppressor p53 and other factors and prevention of chemically-induced oxidative stress, aging, and cancer. The NQO1 and NQO2-null mice generated in our laboratory showed increased sensitivity to chemical carcinogenesis. Approaches include NQO1/NQO2-p53 interaction, apoptosis, cellular proliferation and differentiation, microarray, proteomics, and carcinogenesis studies. The second position will study the mechanisms of signal transduction in antioxidant induction of drug-metabolizing enzyme genes expression. Approaches include gene manipulation, transfection, nuclear translocation, immunoprecipitation, and protein-protein interactions. Salaries are competitive and negotiable. Applicants should submit curriculum vitae, names, addresses, telephone numbers, and e-mail addresses of three references to: **Dr. Anil K. Jaiswal, Ph.D., Professor, Department of Pharmacology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, U.S.A.,** or **e-mail: ajaiswal@bcm.tmc.edu.**

Baylor College of Medicine is an Equal Opportunity, Affirmative Action, and Equal Access Employer.

POSTDOCTORAL FELLOW/RESEARCH FACULTY

Department of Biochemistry and Molecular Biology
Thomas Jefferson University
Philadelphia, Pennsylvania

NIH-funded position is available to study the biological role of receptors, receptor kinases, and arrestins in *C. elegans*. Specific projects are focused on the role of receptor kinases and arrestins in chemosensation and development. Applicants should have a Ph.D. and/or M.D. and have experience using *C. elegans* as a model organism.

Interested applicants should send curriculum vitae, a statement of research interests, and a list of three references to:

Dr. Jeffrey L. Benovic, Chair
Department of Biochemistry and Molecular Biology
Thomas Jefferson University
233 South 10th Street
Philadelphia, PA 19107
E-mail: benovic@mail.jci.tju.edu

Equal Opportunity Employer.

FACULTY POSITIONS

Program in Cell Stress and Cancer Nanomedicine
Simmons Comprehensive Cancer Center
University of Texas Southwestern Medical Center Dallas

Tenure-track to tenured faculty positions at the levels of Assistant, Associate or Full Professor are available to qualified candidates in the areas of DNA repair signaling, stress-inducible gene/protein responses, apoptosis, tumor suppressor signaling/function (e.g., AKT/PTEN, NF-KB, Hdm-2, p53, pRb), insulin-like growth factor (IGF) -1R/EGFR signal transduction, drug and small interfering RNA (siRNA) delivery, cancer molecular imaging, and cancer nanomedicine. Successful candidates will join an interactive group of investigators studying molecular stress responses in combination with novel nanotechnology drug delivery. Applicants should submit a cover letter outlining research interests, curriculum vitae, and a list of three references to: **David A. Boothman, Ph.D., Robert B. and Virginia Payne Professor of Oncology, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Y4.206, Dallas, TX 75390-8807.**

University of Texas Southwestern is an Equal Opportunity/Affirmative Action Employer.

The Princeton Institute for the Science and Technology of Materials (PRISM) seeks a distinguished **FACULTY MEMBER** in the general area of materials, nanostructures, and photonics. The ideal candidate will have an outstanding national reputation in innovative research and teaching, and will provide transformative leadership in Princeton's School of Engineering and Applied Science. Appointments will be made through PRISM and appropriate academic departments in engineering and the applied sciences such as Chemical Engineering, Civil and Environmental Engineering, Electrical Engineering, Mechanical and Aerospace Engineering, Chemistry, Geosciences, and Physics. Please send a complete resume, a description of research and teaching interests, and names of three references to: **Professor James C. Sturm, Director, PRISM, 320 Bowen Hall, Princeton University, Princeton, NJ 08540.** Application material should be sent as soon as possible. *Princeton is an Equal Opportunity/Affirmative Action Employer. For information about applying to Princeton and how to self-identify, please link to* **website: http://web.princeton.edu/sites/dof/ApplicantsInfo.htm.**

ZOOLOGIST

The Biology Department at Saint Joseph's University invites applications for a tenure-track **ASSISTANT PROFESSOR** position. Applicants should be broadly trained in zoology, with specialization in invertebrate biology preferred, possess a Ph.D., and have a commitment to undergraduate education. Teaching responsibilities include offering an upper-division and/or Master's-level course relating to the area of expertise, teaching in an introductory biology course sequence and nonmajor service courses as needed. Biology faculty also advise students and serve on University and departmental committees. The successful candidate will have good communication skills and include students in a productive research program. Further information about the Department can be found at **website: http://www.sju.edu/biology.** Applications must be submitted online at **website: http://www.sju.edu/hr**; click on Employment, and follow the instructions. Applications are to include a letter of introduction, a complete curriculum vitae, a statement of research interest and major equipment needs, and a statement describing your teaching philosophy. Three letters of reference and copies of transcripts should be sent to:

Dr. Paul Tefft
Chair, Biology Department
Saint Joseph's University
5600 City Avenue
Philadelphia, PA 19131
E-mail: *ptefft@sju.edu*

Review of candidate files will begin January 15, 2006. Applications will be accepted until the position is filled. *Saint Joseph's University is a private, Catholic, and Jesuit institution and expects members of its community to be knowledgeable about its mission and make positive contributions to that mission. Affirmative Action/Equal Opportunity Employer. Minorities/Females/Veterans/Persons with Disabilities.*

POSTDOCTORAL POSITIONS

Keck Graduate Institute

Two two-year positions are available immediately for research focused on DNA bioassay and biosensor development using nanoscale materials and isothermal nucleic acid amplification. Position One requires expertise in analytical chemistry, molecular biology and enzymology (particularly restriction endonucleases, polymerases, and cloning/ mutagenesis), assay optimization and validation. Position Two requires expertise in electrochemistry (impedance spectroscopy), colloid and surface chemistry, strong instrumental background (atomic force microscopy, general surface characterization techniques), basic proficiency in microfabrication, fundamental knowledge of biochemistry and molecular biology. Both positions require good written and oral communication skills, ability to work independently and be self-motivated in an interdisciplinary team environment. The Keck Graduate Institute **(website: http://www.kgi.edu),** a member of The Claremont Colleges, is located 30 miles east of Los Angeles. Mail cover letter and curriculum vitae to: **Dr. Angelika Niemz, Keck Graduate Institute, 535 Watson Drive, Claremont, CA 91711. Fax: 909-607-9826. E-mail: aniemz@kgi.edu.** *Equal Opportunity Employer.*

POSTDOCTORAL POSITION

Postdoctoral position is available to study cell and molecular biology of complications of diabetes mellitus and kidney development. Potential candidates must have documented experience of one or more years in cell and molecular biology techniques. Please send curriculum vitae with three references to: **Yashpal S. Kanwar, M.D., Ph.D., Northwestern University Medical School, 303 E. Chicago Avenue, Chicago, IL 60611 U.S.A. E-mail: y-kanwar@northwestern.edu.**

FELLOWSHIPS

Friedrich-Schiller-University

Max Planck Institute for Chemical Ecology

HKI

International Max Planck Research School

"*The Exploration of Ecological Interactions with Molecular and Chemical Techniques*"

20 PhD Fellowships in Molecular and Chemical Ecology

The International Max Planck Research School (IMPRS) on

"*The Exploration of Ecological Interactions with Molecular and Chemical Techniques*"

in Jena, Germany, is the first graduate school worldwide where modern chemical and molecular techniques are systematically linked to ecological research.
The research school offers 20 PhD fellowships in molecular biology, ecology, entomology, microbiology or (bio)-chemistry, beginning in July 2006.
Students holding a Master's degree (or equivalent) from any national and international university with a proven record of success in one of the relevant disciplines and being interested in examining traits of ecological interactions are eligible to conduct a doctoral project within the IMPRS. Courses of the IMPRS are held in English.
Application deadline is **January 15, 2006.**

For detailed information on the IMPRS, the application and admission procedures in Jena please visit our website **http://imprs-jena.ice.mpg.de/**

MAX-PLANCK-GESELLSCHAFT

11th Prouts Neck Prostate Cancer Meeting "EMERGING STRATEGIES IN PROSTATE CANCER THERAPY" November 2-5, 2006 Black Pointe Inn/Prouts Neck, Maine

The goal of the Prouts Neck Prostate Cancer Meeting is to assemble a multidisciplinary group of senior and young investigators to discuss fundamental questions related to the field. These meetings are structured in such a fashion to generate discussion from all of the participants. On behalf of the Program Committee, we urge all "Young Investigators" to submit an application for attendance at this very important meeting. For accepted participants, all expenses associated with attendance will be covered. The meeting is limited to 75 participants. Please forward your name, title and an abstract of your presentation. Deadline for receipt of information is no later than **March 15, 2006**.

This meeting is dedicated to the participation of women and minorities.

Send your request to:

Robert H. Getzenberg, Ph.D.
Brady Urological Institute
600 N Wolfe St
Marburg 121
Baltimore, MD 21287

Support by NCI CA 97015

AWARDS

Children's Tumor Foundation
Ending Neurofibromatosis Through Research

Neurofibromatosis (NF) includes NF1, NF2 and schwannomatosis and can cause potentially fatal neurological tumors as well as deafness, vision loss, learning disabilities and bone deformities. NF affects 100,000 persons in the US. Areas of NF research include tumor signal transduction; cell lineage and differentiation; molecular genetics; mechanisms and management of pain; and cognitive function. Children's Tumor Foundation is committed to ending neurofibromatosis through research.

CALL FOR ABSTRACTS AND SPONSORSHIP ANNOUNCEMENT
ANNUAL NF CONSORTIUM MEETING
JUNE 4-7, 2006: ASPEN, COLORADO

Abstracts are invited for this annual forum, the premier annual NF-focused research meeting. Abstracts may be selected for platform presentation and meeting sponsorship (travel and hotel costs paid). Other abstracts will be eligible for poster presentation.

Abstracts Submission Deadline: March 15, 2006

Registration and Abstract Forms: http://www.ctf.org/professionals/meetings.htm. Further information: Min Wong, Research Coordinator (email: **mwong@ctf.org**)

CTF YOUNG INVESTIGATOR AWARDS 2006:
FINAL ANNOUNCEMENT

Young Investigator Awards support pre- and postdoctoral researchers to focus on NF research. Applications in basic, translational or clinical research are welcome. Awards offer two-year NIH-equivalent levels of funding up to $45,000/year plus travel to NF Annual Consortium and other meetings.

Intent to submit application (first 2 pages) due: February 14, 2006
Full application due: April 1, 2006

Full RFA and application materials: http://www.ctf.org/professionals/yia.htm. Further information: **Cicely Acosta**, Grants Administrator (email: **cacosta@ctf.org**)

CONFERENCE

MDC Berlin-Buch

HELMHOLTZ GEMEINSCHAFT

MDC International Conference on Epithelial Organization and Organ Development

May 11–14, 2006, Berlin, Germany

Confirmed Speakers

W. Birchmeier - Berlin, Germany
H. Clevers - Utrecht, The Netherlands
F. Constantini - New York, USA
I. Drummond - Charlestown, USA
M. Hebrok - San Francisco, USA
Y.N. Jan - San Francisco, USA
K. Kästner - Philadelphia, USA
E. Knust - Düsseldorf, Germany
M. Labouesse - Illkirch, France
A. McMahon - Boston, USA
K. Mostov - San Francisco, USA
N. Perrimon - Boston, USA
C. Samakovlis - Stockholm, Sweden
A. Schedl - Nice, France
R. Shivdasani - Boston, USA
L. Solnica-Krezel - Nashville, USA
D. Stainier - San Francisco, USA
L. Sussel - Denver, USA
S. Vainio - Oulu, Finland
B. Weinstein - Bethesda, USA
M. Zerial - Dresden, Germany

Sessions

- Formation and Function of Epithelial Layers
- Branching Morphogenesis
- Epithelial to Mesenchymal Transition
- Organ Development: Kidney, Pancreas, Liver, and Intestine Stem Cells/Regeneration

The Symposium will be held in Berlin-Buch on the Campus of the Max Delbrueck Center for Molecular Medicine.

Online Registration and Information at:
http://mdc-symposium2006.de/

Local Organizers

Salim Abdelilah-Seyfried
Carmen Birchmeier-Kohler
Walter Birchmeier
Thomas Willnow

Contact

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POSITIONS OPEN

University of California, San Francisco (UCSF) Department of Ophthalmology is recruiting for a **POSTDOCTORAL POSITION** for work on a new medical device for the modulation of muscle activity in chronic applications. The applicant will be joining a world class team of researchers including physicians from UCSF and Engineers from University of California, Berkeley and University of California, Santa Cruz.

Responsibilities: Design and fabricate microelectromechanical systems (MEMS) chips and associated system components for direct clinical application. Collaborate with a diverse multidisciplinary team.

Requirements: Ph.D. in bioengineering, electrical engineering, or related discipline. Hands-on experience in MEMS device design and fabrication. Experience with microfluidics a strong advantage. Background in integration of sensors and wireless technology a plus. Background knowledge in muscle physiology a plus. Good verbal, written, and interpersonal communication skills essential.

Please e-mail cover letter and curriculum vitae to **Anthony Liu** at **e-mail: anthony.liu@ucsf.edu.**

CANADA RESEARCH CHAIR TIER II
Faculty of Science, University of Regina
Water and Environment, Tenure-Track Position

Tenure-track position with water and the environment research focus at the University of Regina. Nominee will be sponsored for a Canada Research Chair Tier II per eligibility criteria (**website: www.chairs.gc.ca**). Potential areas of expertise include groundwater, geofluids, limnology, biogeochemistry, environmental chemistry, aquatic contaminants, atmospheric processes, or allied fields. We have laboratories of stable isotope technology, mass spectrometric analysis of trace contaminants, geofluid analyses, and analytical computation, and a $52 million building addition will open May 2007. Successful candidate must have Ph.D. with an excellent research record and will establish a nationally competitive research program while teaching a limited number of courses. Application deadline is 13 February 2006. Details at **website: http://www.uregina.ca./science.**

POSTDOCTORAL POSITION AVAILABLE
Washington University, St. Louis, Missouri

We have an immediate opening for a Postdoctoral Research Associate in the Department of Obstetrics and Gynecology, Perinatal Biology Lab. Our research focuses on the mechanisms of placental development and function. Utilizing molecular and biochemical approaches we analyze proteins that regulate trophoblast differentiation and adaption to injury. Applicants should have a Ph.D. degree, and exhibit interest and preferably expertise in modern gene expression technology and informatics. *Applicants must be United States citizens or have a permanent resident status to be eligible for support by a T32 training grant.* Send curriculum vitae, research experience, and names of two references to: **Yoel Sadovsky M.D., Washington University, Department of Obstetrics and Gynecology–Campus Box 8064, 4566 Scott Avenue, St. Louis, MO 63110. E-mail: ysadovsky@wustl.edu.** *Washington University is an Equal Opportunity/Affirmative Action Employer.*

NIH-funded POSTDOCTORAL RESEARCH POSITIONS are available to study the role of the p200-family proteins in mouse models of lupus disease. Candidates must have a Ph. D. degree with demonstrated research experience in molecular immunology. Evidence of appropriate research training with a record of publications in peer-reviewed journals is required. Additionally, experience in working with mice is highly desirable. Contact: **Divaker Choubey, Ph. D., Department of Radiation Oncology, Loyola University Chicago, Maywood, IL. E-mail: dchoube@lumc.edu. Telephone: 708-202-8387, extension 23407.**

POSITIONS OPEN

EXECUTIVE VICE PRESIDENT OF RESEARCH

National Disease Research Interchange (NDRI), a not-for-profit company providing scientists with human biomaterials for research, invites applications for Executive Vice President of Research. The Executive Vice President will be the chief operating officer of the organization, managing an experienced staff of scientific professionals. A key responsibility will be ensuring that technologies are managed, leveraged, and marketed to potential partners and licensees consistent with the organization's mission.

The Executive Vice President of Research will be responsible for the overall scientific direction of the organization and supervise the Research Department to include: reviewing research applications, tracking service to researchers, identifying researcher trends, exhibiting and presenting at scientific meetings and preparing progress reports, as well as other written presentation materials. In addition, the Vice President of Research will be a key member of the senior team and be responsible for the identification of appropriate grant opportunities as well as the preparation of those grant applications.

Qualified candidates will have a Ph.D. in molecular biology, immunology, genetics, pathology or a related field and are expected to have submitted successful grant applications to NIH, be familiar with NIH reporting requirements and have strong project management experience. Biotech and tech transfer experience required. Computer expertise to include advanced spreadsheet, database, and reporting skills. Must have excellent analytic, writing, and presentation skills. An energetic team player committed to organizational growth and identification of new opportunities is required. Competitive salary and excellent benefits. E-mail curriculum vitae to **e-mail: jobs@ndriresource.org** or mail to: **National Disease Research Interchange, 1628 JFK Boulevard, 8 Penn Center, 8th Floor, Philadelphia, PA 19103, Attn: S. McGovern.**

ANNOUNCEMENTS

FIRST CALL FOR PROPOSAL-2006
INDO-U.S. SCIENCE AND TECHNOLOGY FORUM
Fulbright House, 12 Hailey Road,
New Delhi-110 001, India
Website: http://www.indousstf.org

The Indo-U.S. Science and Technology Forum (Forum), established under an agreement between the governments of India and the United States of America, is an autonomous, not-for-profit society that promotes and catalyzes the Indo-U.S. bilateral collaborations in science, technology, engineering, and biomedical research through substantive interaction among government, academia, and industry.

The Forum seeks to support innovative programs aimed to stimulate interactions that have a strong potential for generating follow-on activities and building long-term Indo-U.S. science and technology relationships. The Forum promotes a program that nurtures contacts between young and mid career scientists and technologists and fosters active public-private partnership in R&D.

The Forum solicits proposals on a four-monthly cycle (January, May, September) jointly submitted by the U.S. and Indian principal investigators from academia, government funded institutions/laboratories, and private R&D entities for: (1) Knowledge R&D Networked and Public-Private Networked Indo-U.S. Centers; (2) Bilateral workshops, conferences, symposia, schools, etc.; (3) Travel grants: (a) to avail already awarded fellowship and sabbatical positions in U.S./India; (b) for selected U.S. participants to attend international conferences/events in India; (c) for specific exploratory/planning visits aimed at large-scale collaborations.

Detailed format available at **website: http://www.indousstf.org.** For further details and electronic submission, contact: **Arabinda Mitra, e-mail: amitra@indousstf.org; and Michael Cheetham, e-mail: mcheetham@si.edu.**

Submission deadline is 28 February 2006, and award announcement is mid May 2006.

POSITIONS OPEN

CARDIOVASCULAR SCIENTIST
Department of Pharmacology, Physiology and Toxicology
Joan C. Edwards School of Medicine
Marshall University

Applications are invited at the **ASSISTANT** or **ASSOCIATE PROFESSOR** level for a tenure-track faculty position in the Department of Pharmacology, Physiology and Toxicology. Applicants should conduct research on the molecular or genetic basis of cardiovascular disease and should currently have a nationally funded research program in this area. The successful candidate will participate in the activities of the Department and will contribute expertise to the West Virginia IDeA Network of Biomedical Research Excellence (WV-INBRE) program. WV-INBRE is an NIH-funded multi-institutional program with a research theme in cellular and molecular biology and a focus on cardiovascular disease.

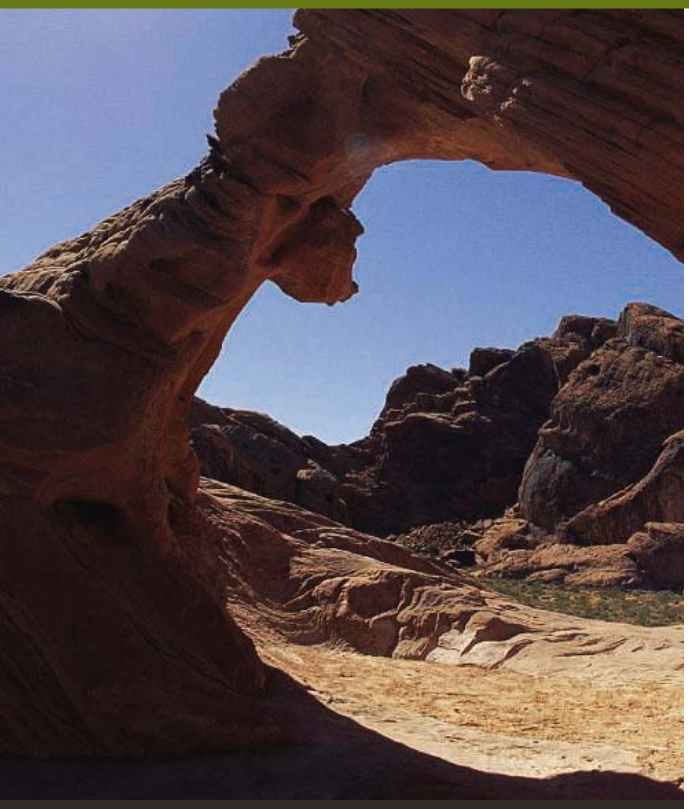
Applicants should send curriculum vitae, statement of research interests and funding source(s), and the names and contact information for at least three references to:

Chair of the Search Committee
Dr. Gary O. Rankin
Department of Pharmacology
Physiology and Toxicology
Joan C. Edwards School of Medicine
Marshall University
1542 Spring Valley Drive
Huntington, WV 25704-9310
E-mail: rankin@marshall.edu
Fax: 304-696-7391

Applications will be accepted until the position is filled. *Marshall University is an Equal Opportunity/Affirmative Action Employer.*

MARKETPLACE

Bridge the Gap Between Whole Blood and Successful Gene Expression Profiling



Ambion Offers Integrated Solutions for Gene Expression Profiling from Whole Blood —

- Achieve more reproducible and accurate expression profiling results
- Stabilize the gene expression profile even at ambient temperatures with RNA*later*®
- Prepare blood samples for RNA isolation, including globin reduction, in just minutes
- Accommodates various amounts of blood, from 0.5 mls to >10 mls

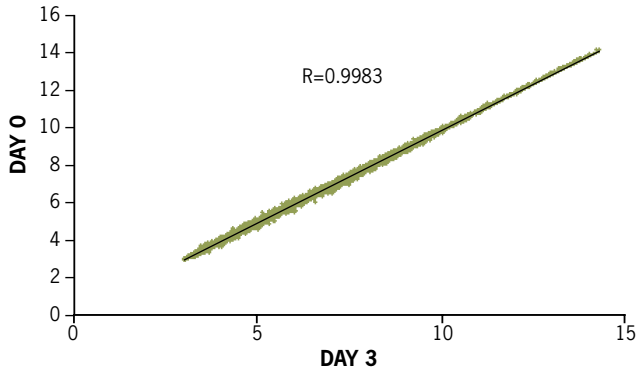
Sample Collection & Stabilization –
- RNA*later*® Tissue Collection: RNA Stabilization Solution
- LeukoLOCK™ Total RNA Isolation System

RNA Isolation –
- RiboPure™ Blood Kit
- LeukoLOCK™ Total RNA Isolation System

Globin mRNA reduction –
- GLOBINclear™ Whole Blood Globin Reduction Kit
- LeukoLOCK™ Total RNA Isolation System

RNA Amplification –
- MessageAmp™ II – Biotin *Enhanced* Single Round aRNA Amplification Kit

www.ambion.com/prod/blood2gene



Samples Stored in LeukoLOCK™ Filters are Ideal for Microarray Analysis. RNA was prepared using the LeukoLOCK Total RNA Isolation System from filtered leukocytes processed immediately or stored on the LeukoLOCK Filter in the presence of RNA*later*® for 3 days at room temperature. Correlation plots from normalized data are shown for array signal intensities for day 0 or day 3 replicates as well as day 0 vs. day 3 comparisons.

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Expanding options for kinase biology

Looking for kinase options to drive your research and discovery projects? We now offer:

- **250+ human kinases and growing**—access the largest collection available
- **14 clinically relevant mutant kinases**—accelerate therapeutic development
- **Z'-LYTE™ Kinase Assay Technology**—screen more than 200 kinases in a single, fluorescent format
- **SelectScreen™ Kinase Profiling Service**—use the fastest growing selectivity profiling service
- **Stealth™ RNAi Human Kinase Collection**—utilize rapid, high-throughput functional screening
- **CellSensor™ cell-based assays**—elucidate signal transduction pathways

Through the integration of BioSource with Invitrogen, we are adding one of the largest collections of signal transduction antibodies, ELISAs, Luminex® reagents, and signaling arrays to our kinase portfolio. No one else offers you more for kinase research and discovery (Table 1).

Table 1—Invitrogen's kinase portfolio offers more choice than the nearest competitor*.

	Invitrogen	Nearest competitor
Distinct, wild type, human protein kinases	237	206
Phospho site-specific antibodies	272	186
Fluorescent assay (FA) platforms	4	2
Protein kinases validated with FA platforms	201	80
Cell lines for pathway analysis	29	0
Protein kinases addressed by RNAi platform	ALL	<100

To learn more about Invitrogen's expanding kinase collection, visit **www.invitrogen.com/drugdiscovery**.

To order BioSource products, visit **www.biosource.com**.

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*All data pulled from competitor's web site as of 11/8/05.